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EFFECTS OF PHENYLBUTAZONE IN GOUT*

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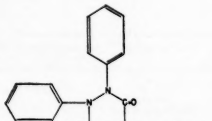
SAN FRANCISCO

PHENYLBUTAZONE (3, 5-dioxo-1, 2-diphenyl-4-n-butyl-pyrazolidin sodium) is a pyrazolon derivative with anti-inflammatory and analgesic properties.[1] Its formula is as follows:



Success with this drug in the treatment of gout has previously been reported by Gutman and Yü,[2] by Kuzell et al.,[3,4] and by Steinbrocker and his associates.[5] In the past year we have observed its effects in 26 male adult patients with gouty arthritis, of whom 10 had acute arthritis and 16 chronic joint disease.

METHODS

Patients with acute arthritis were seen on an outpatient basis; patients with chronic diseases were hospitalized, when indicated, on the medical wards at the Veterans Administration Hospital, San Francisco. In 2 cases metabolic-balance studies were carried out at the University of California Hospital, San Francisco.††

Three preparations of phenylbutazone‡‡ were utilized in treatment: 20 per cent aqueous solution for intramuscular injection, and capsules or enteric-coated tablets of 200 mg. each for oral administration.

The concentration of phenylbutazone in the serum was determined by extraction with heptane, transferred to two and five-tenths normal solution of sodium hydroxide, and the optical density estimated at 265 millimicrons.§§ Determination of 17-hydroxycorticoids was performed by a modification of the method of Reddy, Jenkins and Thorn.[6] Urinary 17-ketosteroid concentrations were ascertained by the method of Callow et al.[7] Urinary creatinine, chloride, and urinary and serum uric acid concentrations were calculated by standard laboratory methods.

ACUTE GOUTY ARTHRITIS

Ten patients with acute gouty arthritis were selected for study on the basis of the following criteria: acute onset of the disease; monarthritis or oligoarthritis; signs of local inflammation; elevated uric acid levels in serum; recurrent attacks, with previous response to colchicine; and remissions between attacks. They ranged in age from twenty-seven to sixty-four years and had had recurrent symptoms for three to fifteen years. These patients were treated with phenylbutazone during 20 acute attacks. The daily dose was 0.8 to 1.0 gm., given intramuscularly or orally. In 15 of the attacks symptoms had been present less than five days when phenylbutazone was started. The

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‡‡Phenylbutazone (Butazolidin), was kindly supplied by Dr. Albert Hemming, medical director, Geigy Pharmaceuticals.

§§Details of this method were made available to us by Geigy Pharmaceuticals, 220 Church Street, New York 13, New York.

other 5 were of seven to fourteen days' duration when this drug was administered. Treatment was continued until objective signs of arthritis disappeared.

In 19 of the 20 attacks subjective relief of pain occurred within twenty-four hours of the beginning of treatment. Disappearance of all objective signs was considerably slower; joint effusions were the last to subside. In 16 of the 20 episodes signs of inflammation abated within five days. In 1 case joint inflammation persisted, despite the administration of phenylbutazone. After eleven days this attack was finally terminated with colchicine. The details of response to treatment in this group are summarized in Table 1.

The therapeutic effects of phenylbutazone compared favorably with those of colchicine. In addition,

TABLE 1. *Results of Treatment of Acute Gouty Arthritis (20 Attacks) with Phenylbutazone.*

RESULT	INTERVAL BEFORE RESPONSE	NO. OF ATTACKS
	days	
Subjective relief	1	19
	4	1
Disappearance of all objective signs	5	16
	5 to 9	3
Incomplete response	11	1

it was preferred because of the absence of the severe gastrointestinal disturbance that frequently attended the use of colchicine. Two acute episodes were terminated with phenylbutazone after colchicine had only partially alleviated the symptoms despite its administration to the point of diarrhea. Relapse after withdrawal of the drug, which we had observed in 1 of 3 similar patients treated with cortisone or ACTH, did not occur in this group of subjects.

CHRONIC GOUTY ARTHRITIS

The second group consisted of 16 patients with gouty arthritis that had become chronic, who, in recent months or years, had never been entirely free of joint symptoms. They ranged in age from thirty-one to sixty-four years, and the duration of their gouty symptoms varied from three to thirty-three years. These patients also showed in one joint or more at least two of the following: limitation of motion; deformity; and persistent signs of inflammation, such as those of synovitis. Eight subjects of this group were partially or totally disabled. Thirteen had multiple tophi. Despite various prophylactic and therapeutic regimens, the clinical course had been progressively unfavorable.

The minimal effective daily dose of phenylbutazone varied between 0.4 and 1.0 gm. administered orally (0.4 gm. in 1 patient, 0.6 gm. in 11 patients, 0.8 gm. in 3 patients, and 1.0 gm. in 1 patient); it was given continuously for one to eleven months (average, six and a half months).

In all cases subjective discomfort was greatly reduced, and considerable functional improvement occurred, exceeding that obtained with other drugs used in safe pharmacologic dosage. The most impressive objective improvement was the decrease of signs of articular inflammation. Fixed deformities were not significantly changed. Of the 8 disabled patients, 7 were able to return to work.

To evaluate the effects of phenylbutazone the number of gouty exacerbations manifested by inflammation of the joints was recorded during the treatment period and during an equivalent period immediately before therapy in each case. The decrease of exacerbations during treatment with phenylbutazone was impressive (Table 2). Most of the mild inflammatory relapses during treatment appeared when we attempted to establish the minimal effective dose by progressively decreasing the amount to the point where the patient suffered slight discomfort. One patient experienced a severe exacerbation of gout despite a daily maintenance dose of 1.0 gm. Although tophi occasionally became softer during treatment,

TABLE 2. *Exacerbations in 16 Patients with Chronic Gouty Arthritis before and during Treatment with Phenylbutazone.*

PERIOD	NO. OF SEVERE EXACERBATIONS	NO. OF MILD EXACERBATIONS
Before treatment	60	Too numerous to count
During treatment	3	20 (most occurred on minimal effective dose)

they did not decrease in size. In 1 patient a new tophus appeared during the fourth month of continuous treatment.

TOXICITY

Undesirable side effects of phenylbutazone among the patients with acute gouty arthritis were of no consequence. Serious toxic effects were observed in 9 of the 16 patients with chronic gouty arthritis. Withdrawal of the drug was necessary in 3 cases because of uncontrolled nausea and vomiting (1 patient), aggravation of a pre-existing duodenal ulcer (1 patient) and severe stomatitis (1 patient). In 2 patients with concurrent arteriosclerotic heart disease the occurrence of dyspnea and edema, which had not previously been experienced, required the use of diuretics.

Blood counts were done at least twice a week in the early periods of treatment and once a week thereafter. Toxic effects on the hematopoietic system were not observed.

Evidence of toxicity usually occurred during the first few weeks of treatment. In the patient with

stomatitis, however, the fact that the symptoms did not develop until the fourth month of therapy emphasizes the need for unremitting caution in the administration of phenylbutazone.

The undesirable side effects are summarized in Table 3.

Absorption and Excretion

The rate of absorption and excretion of phenylbutazone was studied in 9 hospitalized patients who had not previously received the drug. Serum concentrations in 8 patients on long-term maintenance therapy were determined in an attempt to establish therapeutic range.

As early as fifteen minutes after a single oral dose of 0.2 gm. detectable amounts of phenylbutazone were found in the blood and urine. Serum levels were determined at intervals of fifteen minutes, one hour, four hours, and twenty-four hours after single doses of 0.2, 0.4 and 1.0 gm. administered either orally or intramuscularly. In all cases the levels were proportionate to doses and rose to a peak at four hours, and then declined in twenty-four hours to levels between those previously obtained fifteen minutes and one hour after administration of the drug (Fig. 1).

Table 3. *Undesirable Effects of Phenylbutazone in 9 of 16 Patients with Chronic Gouty Arthritis Treated for One to Eleven Months.*

Side Effect	No. of Cases
Epigastric distress	4
Nausea and vomiting	1*
Bleeding from peptic ulcer	1†
Edema	2
Dyspnea	2
Stomatitis	1‡
Rash	1

*Drug discontinued on 34th day.
†Drug discontinued on 229th day.
‡Drug discontinued on 216th day.

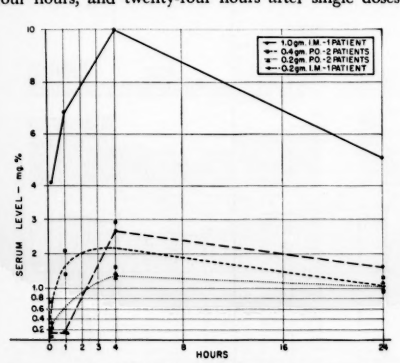

Figure 1. *Serum Phenylbutazone Levels after Single Doses Orally and Intramuscularly.*

The blood levels obtained in 8 patients receiving the minimal constant dose required to keep them relatively free of symptoms varied from 5.8 to 18.7 mg. per 100 cc. These levels were not always proportionate to the maintenance dose. For example, in patient Bur. oral administration of 0.6 gm. a day resulted in a level of 5.8 mg. per 100 cc. of serum, whereas in patient Sch. 0.4 gm. a day, given orally, resulted in a level of 18.7 mg. per 100 cc. The reason for such a variation was not apparent. No renal lesion was demonstrable in Sch. A chart of maintenance doses and blood levels is presented in Table 4.

Table 4. *Serum Phenylbutazone Levels during Maintenance Therapy.*

Patient	Daily Dosage	Serum Phenylbutazone
	gm.	*mg./100 cc.*
Sch.	0.4	18.7
Bur.	0.6	5.8
Bet.	0.6	6.1
Fav.	0.6	5.9
Lan.	0.6	13.1
Tim.	0.6	13.8
Den.	0.6	8.6
Den.	0.8	16.0
Beh.	0.8	15.3

The slow rate of excretion of phenylbutazone after long-term treatment was demonstrated in 1 patient

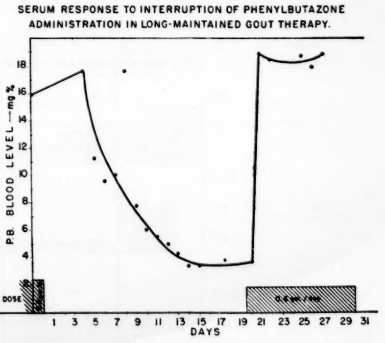
SERUM RESPONSE TO INTERRUPTION OF PHENYLBUTAZONE ADMINISTRATION IN LONG-MAINTAINED GOUT THERAPY.
PB. BLOOD LEVEL — mg %
PB. DOSE
0.6 GM. / DAY
DAYS

Figure 2. *Serum Response to Interruption of Phenylbutazone Administration in Long-Maintained Therapy of Gout.*

(Den.). After several months of maintenance therapy with 0.6 gm. phenylbutazone daily, by mouth, the dose was adjusted to 0.8 gm.; four days later the drug was discontinued. Daily serum phenylbutazone levels were determined. During the first fifteen days after the drug had been withdrawn, the level declined progressively to approximately 3.5 mg. per 100 cc., where it remained for an additional five days (Fig. 2). After twenty days a relapse occurred, and the drug was resumed in a dosage of 0.6 gm. a day.

Metabolic Observations

Certain metabolic observations were made. A reduction in serum uric acid concentration occurred in each of the 16 patients tested, ranging from 1 to 5.7 mg. per 100 cc., with an average decrease of 3.1 mg. per 100 cc. (Fig. 3).

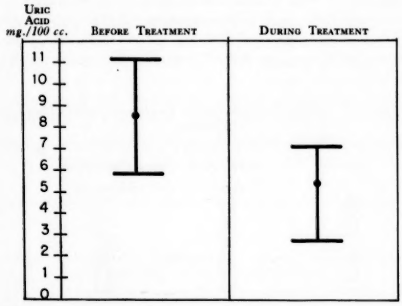

Figure 3. *Change in Serum Uric Acid in 16 Patients with Chronic Gouty Arthritis Treated with Phenylbutazone. The range of fall was 1-5.7 mg. per 100 cc., with an average reduction of 3.1 mg. per 100 cc.*

Two patients were subjects of metabolic-balance studies on constant dietary intake before and during administration of 1 gm. daily for four or five days are shown in Figure 4 and Tables 5 and 6.

The depressed excretion of nearly all the urinary constituents tested, including creatinine, strongly suggests that phenylbutazone acts directly on the kidney. The retention of sodium and hydrocortisone-like substances was the most noticeable. The decrease in uric acid output was accompanied by a fall in concentration of uric acid in the serum. Similarly, we did not find an increase in urinary uric acid that could account for the drop in serum uric acid in any of our other cases. Control studies showed that the lower serum levels were real and not simply the result of interference by phenylbutazone with the laboratory determination of uric acid.

Suppression of the output of urinary steroids after prolonged use of phenylbutazone (more than six months on 0.6 gm. daily) appears only slowly reversible. Thus, in patient Den. the excretion of 17-hydroxycorticoids and 17-ketosteroids was still below the control values a week after prolonged therapy had been discontinued (Table 7). This, however, was most probably related to the slow excretion of phenylbutazone from such a patient, as noted above and in Figure 2.

There was no significant alteration in the number of circulating eosinophils during phenylbutazone therapy.

In concurrent studies temporary suppression of I^{131} uptake by the thyroid gland during phenylbutazone therapy was demonstrated in these patients[8,9] and confirmed in animal experiments.[10]

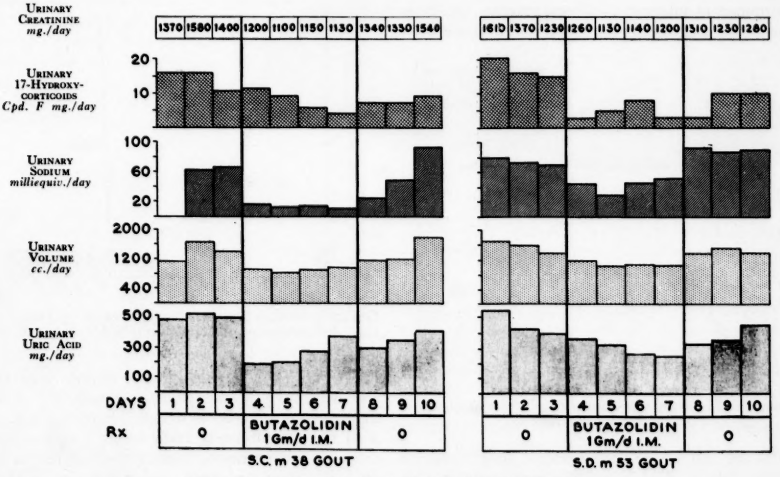

Figure 4. *Excretory Changes in 2 Patients on Constant Diets.*

Discussion

Our results indicate that phenylbutazone is effective not only in the control of acute gouty arthritis but also in the suppression of chronic gouty arthritis.

The mechanism of its therapeutic action remains speculative. Although the drug is known to be analgesic and anti-inflammatory, these factors cannot account entirely for its efficacy in gout, since in our experience other painful and inflammatory conditions were less responsive. Its mode of action is apparently not mediated through a pituitary-adrenal-stimulating mechanism since the number of circulating eosinophils is unaffected during phenylbutazone administration, whereas the urinary excretion of adrenal corticoids and ketosteroids is depressed. The sodium retention that occurs presumably results from a direct action of the drug on the renal tubules. These findings support similar observations reported by Rechenberg.[11]

The consistent diminution in the concentration of uric acid in the serum during administration of phenylbutazone is of particular interest. The fact that uricosuria was not accelerated concurrently implied a decrease in uric acid production. This phenomenon prompted a study of the effects of phenylbutazone on nucleoprotein metabolism by Delfel and Griffin.[12] Results of their experiments with radioactive phosphorus tracers in rats suggested that the rate of production of uric acid from nucleic acid was reduced by the influence of phenylbutazone. Even if this same phenomenon occurs in man, however, it is not necessarily related to the clinical effects of the drug in gouty arthritis.

The frequency of toxic effects in our patients (9 reactions in 26 cases) corresponds to that reported by other investigators. The reported incidence of undesirable reactions to phenylbutazone has varied between 23 and 44 per cent.[3-5] These have included edema, vertigo and toxic effects on the skin, the gastrointestinal tract and the hematopoietic system. In general the longer the drug is given, the higher the incidence of toxicity. It is not surprising, therefore, that an unusually high rate of undesirable reactions occurred among our patients who were given long-term treatment for chronic gouty arthritis. The fact that phenylbutazone is excreted slowly may be related to the severity of its toxic effects.

Table 5. *Metabolic Effects of Phenylbutazone in S.D., a Fifty-Three-Year-Old Man, on a Constant Diet.*

Day	Dosage	Urinary Volume	Urinary Constituents					Serum Uric Acid
			uric acid	17-hydroxy-corticoids*	17-ketosteroids	sodium	potassium	
	gm.	*cc.*	*mg./24 hr.*	*mg. "F"/24 hr.*	*mg./24 hr.*	*milliequiv./24 hr.*	*milliequiv./24 hr.*	*mg./100 cc.*
1	—	1680	505	21	11.7	80	52	7.8
2	—	1580	426	16	8.6	75	47	7.5
3	—	1370	400	15	5.5	71	41	7.9
4	1 (intramuscularly)	1190	370	2	6.0	44	49	7.8
5	1 (intramuscularly)	1050	320	5	11.2	38	40	7.4
6	1 (intramuscularly)	1080	268	8	4.4	45	41	7.7
7	1 (intramuscularly)	1060	257	3	4.9	53	48	6.6
8	—	1390	330	3	5.4	92	50	6.0
9	—	1500	360	10	6.5	87	55	5.6
10	—	1440	455	10	5.3	89	50	5.9

*Determined by modification of method of Reddy et al.,[6] in which normal value for males is 10 ± 5 mg. "F" per 24 hours.

Table 6. *Metabolic Effects of Phenylbutazone in S.C., a Thirty-Eight-Year-Old Man, on a Constant Diet.*

Day	Dosage	Urinary Volume	Urinary Constituents							Serum Uric Acid
			creatinine	uric acid	17-hydroxy-corticoids*	17-keto-steroids	sodium	potassium	chloride	
	gm.	*cc.*	*mg./24 hr.*	*mg./24 hr.*	*mg. "F"/24 hr.*	*mg./24 hr.*	*milliequiv./24 hr.*	*milliequiv./24 hr.*	*milliequiv./24 hr.*	*mg./100 cc.*
1	—	—	—	—	—	—	—	—	—	9.0
2	—	—	—	—	—	—	—	—	—	9.2
3	—	—	—	—	—	—	—	—	—	—
4	—	1120	1370	465	16.0	9.0	—	—	—	—
5	—	1620	1580	510	16.0	8.0	63	41	66	—
6	—	1440	1400	480	11.0	8.0	66	42	61	—
7	1 (intramuscularly)	940	1200	195	12.0	7.0	17	34	17	—
8	1 (intramuscularly)	850	1100	200	9.0	6.0	13	31	12	6.9
9	1 (intramuscularly)	940	1150	280	5.8	6.0	14	29	13	6.0
10	1 (intramuscularly)	1000	1130	380	4.0	5.5	11	24	12	4.6
11	—	1230	1340	300	7.0	6.2	24	30	29	3.9
12	—	1240	1330	350	7.0	6.3	50	35	60	3.6
13	—	1620	1540	410	9.0	6.7	72	42	89	4.1
14	—	1230	—	—	9.0	7.5	—	—	72	4.6

*Determined by modification of method of Reddy et al.,[6] in which normal value for males is 10 ± 5 mg. "F" per 24 hours.

Although toxic effects on bone marrow did not occur in these patients with gout we have observed agranulocytosis in 2 patients after treatment of rheumatoid arthritis with phenylbutazone. One of these patients died after perforation of the gall bladder coincident with agranulocytosis. Among other patients treated with phenylbutazone for miscellaneous conditions we have observed thrombocytopenia in 4, gastrointestinal hemorrhage in 2 (1 from a gastric ulcer and 1 from ulcerative proctocolitis), hepatitis in 5, with 1 death, myocarditis in 2, with 1 death, and optic neuritis in 2.[13]

TABLE 7. *Delay in Recovery from Suppression of Urinary Steroids After Prolonged Use of Phenylbutazone.*

PERIOD	17-HYDROXYCORTICOIDS *mg. Compound F/day*	17-KETOSTEROIDS *mg. Dihydroisoandrosterone/day*
Control	10.0	7.0
7 days after discontinuance of phenylbutazone	6.9	3.0
8 days after discontinuance of phenylbutazone	7.7	2.4

It is obvious that phenylbutazone is potentially a toxic drug. The risk involved, especially in long-term use, cannot be overemphasized.

SUMMARY AND CONCLUSIONS

Phenylbutazone is clinically effective in the control of acute gouty arthritis and in the suppression of chronic gouty arthritis.

Toxicity was of no consequence in the short-term treatment of 10 patients with acute gouty arthritis. Undesirable toxic reactions were frequent in long-term use, however, occurring in 9 of 16 patients with chronic gouty arthritis.

The mode of action of phenylbutazone remains unexplained, but certain metabolic effects appear significant. The drug decreases the uric acid concentration in the serum while reducing the excretion of most of the urinary constituents — namely, creatinine, 17-hydroxycorticoids, 17-ketosteroids, sodium, potassium, chlorides and uric acid — as well as lowering the urinary volume. Adrenocortical activation is not included as a significant factor in the mode of action of this drug.

Despite its favorable therapeutic effects, we believe that the potential toxicity of phenylbutazone should limit its use to cases of gouty arthritis that are resistant to other established forms of treatment.

We are indebted to Mrs. Dorothy Cahill, Miss Mary Morrow and Miss Kay Hyde for secretarial and editorial assistance.

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DISSECTING ANEURYSM OF THE AORTA

A Diagnostic Approach

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DISSECTING aneurysms have been known for centuries, but they were little more than curiosities until Shennan[1] created interest in the subject with his masterful review in 1934. In 1942 Sailer[2] collected 500 cases from the literature, only 33 of which had been diagnosed during life. Numerous reports since that time have shown that the condition is seen once in about 380 autopsies[3-5] and that an ante-mortem diagnosis is possible in more than half the cases.[6,7] Despite great interest in the subject in various medical centers many practitioners are not familiar with this condition, probably because most of the literature on dissecting aneurysm has appeared in specialty journals. This is unfortunate because the abrupt onset brings most patients to the family doctor initially. The purpose of this paper is to call attention to the frequency of dissecting aneurysms and to outline a diagnostic approach. It is based on the literature in addition to observations on 9 patients seen by us. Five cases were diagnosed during life. Three patients were seen during the past year in a town of 20,000 population. Since the literature now contains a large num-

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ber of detailed case reports, we see no value in individual presentation of these cases.

Pathology

An understanding of the pathology is essential to the recognition of the clinical manifestations. Dissecting aneurysms bear little resemblance to saccular and fusiform aneurysms. Indeed "aneurysm" (that is, tumor or enlargement) of the aorta may scarcely be present in some cases.[8] X-ray films or post-mortem inspection of the aorta in situ often arouses no suspicion of abnormality. The condition occurs when blood enters the wall of the aorta through a rent in the intima and, under pressure, splits or dissects the medial layer longitudinally for a varying distance. Frequently, the entire length of the aorta is involved.

Pre-existing disease of the media, usually medionecrosis cystica[2,8-10] or sometimes arteriosclerosis,[11-13] is essential. Syphilis[14,15] is rarely found. The etiology of medionecrosis cystica is not known, but Schlichter et al.[8] considered it secondary to diseases of the vasa vasorum. Various observations indicate that dissection is preceded by an intramural hematoma from one of the vasa vasorum, and rupture of the intima occurs at this point. About two thirds of the circumference of the aorta is usually involved. As branches of the aorta are encountered by the process they may be "sheared" off, or the dissection may proceed down the media of these vessels. Interference with blood flow in the branches of the aorta accounts for many of the signs and symptoms. If rupture through the adventitia occurs fatal hemorrhage into a body cavity, usually the pericardium,[4,14,16] may result. Re-entry into the lumen of the aorta at a lower level offers a good chance for survival. The dissection tract may cover over with endothelium and function as a blood-carrying conduit. If the process ends blindly in the wall of the aorta subsequent extension is apt to occur sooner or later. The dissection usually begins just beyond the aortic valves or slightly below the origin of the left subclavian artery.[17]

Predisposing Factors

Although cases are reported at every age, including infancy, dissecting aneurysm is usually encountered in patients past forty years of age.[18] Males predominate over females in a ratio of about 2:1 or 3:1. The condition is similar in these respects to coronary occlusion, with which it is most often confused. Some statistics favor Negroes over Caucasians, but no striking racial predisposition is apparent.[17,19] Hypertension or demonstrable heart disease or both are present in almost all cases but this is not as invariable as some authors have implied. Diseases of the aorta such as hypoplasia and coarctation predispose to spontaneous dissection.[20-22] Half the cases in young female patients have occurred during pregnancy or the puerperium.[22] Patients with the congenital physical characteristics of Marfan's syndrome or arachnodactyly show a high incidence of dissecting aneurysms.[17,23] Physical exertion was given much importance in the older literature, but many cases have been reported to occur during repose and sleep. Most authors at present believe that exertion has been overemphasized.[24]

Clinical Picture

Bedside examination yields vital information in the diagnosis of dissecting aneurysm.[6,14,17] Laboratory procedures usually play a negative or minor role. X-ray studies are sometimes very helpful, but rarely suggest or prove the diagnosis. No single observation or laboratory test is conclusive.[6] The dissection of the aorta itself is almost always manifested by abrupt and severe pain. The other signs and symptoms, which depend on changes in the circulation through branches of the aorta, hemorrhage and pressure on adjacent structures, may be many or few. Involvement of multiple systems is highly characteristic of dissecting aneurysm[16,25] as in another arterial disease, polyarteritis nodosa. But the similarity ends there. Dissecting aneurysm is as sudden and dramatic as polyarteritis is subtle and chronic. However, both are great mimickers and hard to prove during life, often leaving the physician with the impression that something is wrong but eludes explanation; he finds himself making multiple diagnoses to explain varied manifestations.

Primary Manifestations

There is almost always pain unless consciousness is lost. Whatever the initial manifestation, it will invariably be abrupt.[26] Pain usually begins in the chest or upper part of the abdomen but frequently radiates widely. The pain, which is at its maximum immediately or soon after onset but may persist for hours, is usually severe, requiring a great deal of morphine even for partial relief. Many adjectives have been offered to describe the pain, such as tearing, cramping, aching, squeezing and crushing. As in most visceral pain, the patient gropes for words since he is unfamiliar with the sensation. The pain most often radiates to the back and down,[3,17] but may appear almost anywhere, as in the flanks, legs, neck, head, shoulders and arms. The variability of radiation accounts for the confusion with other conditions, although a carefully taken history will reveal subtle differences from the pain of coronary occlusion, biliary or renal colic, pancreatitis and so forth. The onset is usually more abrupt than in these conditions. Indeed, most patients can describe preceding events up to a few seconds before onset. If they were talking, the last word or phrase often is recalled.

Secondary Manifestations

For ease of discussion and reference these are grouped under various systems. No patient will have all or even most of them. Usually, however, if the condition is suggested from the primary manifesta-

tions, careful examination and observation will reveal enough signs to strengthen the diagnosis.

Circulatory and pulmonary systems. The blood pressure varies from extremely high to extremely low values. The pulse rate is also quite variable. Most patients present the pale, moist, cold, drawn facies of shock, however, even when the blood pressure is extremely high. This combination is characteristic. Dyspnea and cyanosis are common but usually less prominent than in pulmonary embolism. Extravasations of blood may occur in the pleural cavities (especially the left), pericardium and mediastinum, giving rise to friction rubs or other signs and symptoms. The murmur of aortic insufficiency, caused by deformity of the valve leaflets or ring, occurs in about a fifth of the cases.[17] If it is known that aortic insufficiency was not present before, this sign is almost pathognomonic in a suspected case. Various other murmurs may be heard over the heart and peripheral vessels.[4,27] According to Logue and Sikes[7] pulsation of the sternoclavicular joint is highly specific.

Variation in pulsations of the arteries of the neck and extremities may occur and should be looked for as well as parallel discrepancies in blood pressure. Reduplication of the pulse wave or a dicrotic pulse has been described.[17] Apparently, this is due to altered flow velocity in the false channel. In 1 of our patients there was a reduplication of the sound heard over the right brachial artery when the blood-pressure cuff was inflated but not over the left brachial artery. The pulse wave was equivocally dicrotic in this case.

Signs of marked arterial insufficiency and gangrene may develop in an extremity, simulating arterial embolism.

Hemoptysis, which was present in 3 of our 9 cases, is considerably more frequent than reports in the literature indicate. The hemoptysis is often slight and easily overlooked.

Nervous system. Impaired circulation through aortic branches may result in ischemia of the brain, spinal cord and peripheral nerves, producing neurologic complications in about a third of the cases.[28,29] The percentage is likely to be much higher in patients surviving longer than forty-eight hours. Dizziness, syncope, convulsions, visual disturbances and hemiplegia may result from carotid or innominate involvement. Flaccid paralysis of the lower extremities, with bladder and bowel dysfunction, indicates spinal-cord injury through intercostal and lumbar vessels. Disturbance of the circulation to an extremity may result in weakness, absent reflexes, sensory impairment and paresthesia. There is often widespread involvement, with bizarre findings. Abnormal signs may change markedly or disappear within a few hours. The ephemeral and varying neurologic picture is characteristic and should be of help in diagnosis.

Gastrointestinal tract. Pain in the upper part of the abdomen but not in the chest is frequently seen in dissecting aneurysm, and many patients are considered to have an acute "surgical abdomen."[30] Some are operated on. Nausea, vomiting, diarrhea, melena and distention are common. Elevation of the serum bilirubin and sometimes of the serum amylase values, as well as leukocytosis, makes differentiation from primary intra-abdominal disorders even more difficult at times. These manifestations are due to dissection of or pressure on the arteries of the celiac axis and mesentery. Gangrene of the intestine may occur. One consoling point is the absence of free intraperitoneal gas.

Genitourinary system. When pain is predominantly in the back or flank and radiates down the leg, renal disease may be simulated.[31,32] The common occurrence of hematuria, both gross and microscopical, tends to complete the picture. Many cases of this type are reported in the literature. Albuminuria is frequent. Elevation of the blood nonprotein nitrogen may be due to shock, rapid breakdown of blood, renal ischemia or combinations of these factors.

Course and Miscellaneous Findings

The course of dissecting aneurysm is highly variable. Some patients feel so well on the next day that they will not remain in the hospital, but most remain ill for some days or weeks if they do not die of internal hemorrhage, heart failure or some other complication. The recurrence of pain[6] and shock and new signs and symptoms indicate an extension of the dissection. Extensions are common and occur at any time. Low-grade fever is the rule. Ecchymoses on the back and flanks are sometimes seen from diffusion of blood along deep fascial planes.

Although most patients die, numerous cases of survival with an active life subsequently are described in the literature.[13,15,33] Levinson[17] reported that 26 per cent of his 58 patients survived for three months or longer. Since recovery does not facilitate the diagnosis, statistics probably favor a high mortality rate.

Electrocardiographic Findings

Since most patients have pre-existing heart disease electrocardiographic tracings are usually abnormal, but typical evolving patterns of acute myocardial infarction are rare. Tracings indicative of hypertrophy or "strain" of the left ventricle are the most frequent. Slight leakage of blood into the pericardial sac accounts for the frequency of tracings characteristic of pericardial inflammation.[17] Changes suggesting coronary insufficiency or localized ischemia of the heart muscle[34,35] occur and are easily explained by pressure on the coronary ostia; when they are present aortic insufficiency is apt to be found. Coexisting coronary sclerosis and previous myocardial infarctions are not rare. Bundle-branch block, disturbances of rhythm and many nonspecific changes are seen. Despite published views to the contrary,[36] we believe that dissect-

ing aneurysm of the aorta should rarely be confused with acute myocardial infarction if the electrocardiograms are properly interpreted and correlated with the clinical picture.

X-Ray Findings

Progressive widening of the aortic shadow and diminished or absent aortic pulsations are the most characteristic x-ray findings.[37] Previous films are very helpful. If intimal calcification is present increased thickness of the aortic wall may be detected and is highly characteristic. A "double shadow" from variation in radiologic density of the dissected aorta is occasionally seen. Blood or fluid in the pleural spaces or mediastinum is common. Angiocardiograms[38] are probably helpful but should rarely be used, for obvious reasons. Planograms[39] may be of value and are more feasible. Unfortunately, many patients are too ill for thorough x-ray studies, which should not be done without regard to the patient's safety. Lodwick[12] recently observed that "The diagnosis of dissecting aneurysm can rarely be accomplished by roentgen findings alone, but requires close correlation of history, physical findings, and roentgen examination." If the clinician cannot suggest the diagnosis to the radiologist, the radiologist will rarely suggest the diagnosis to him.

Laboratory Findings

Leukocytosis with increased neutrophils, increased erythrocyte sedimentation rate and slight anemia are the rule but have little specificity. Slight to moderate elevation of the blood nonprotein nitrogen is frequent. Elevation of the serum bilirubin between 1 and 2 mg. per 100 cc. was observed in the 3 of our cases in which it was determined. This is mentioned several times in the literature, but in the majority of cases the test has not been performed. We suspect that it may be elevated often enough to be of considerable diagnostic value. Levinson, Edmeades and Griffith[30] reported an increase in the serum amylase in 2 cases; in 1 there was no apparent involvement of the pancreas.

Case Report

O.J.M.,* a 62-year-old printer, was admitted to the hospital because he had suddenly fallen to the floor unconscious. When he regained consciousness about 20 minutes later he could not move his legs. He had no particular pain but was very apprehensive. The blood pressure was 180/80. The femoral pulsations were normal, and the legs were warm and not discolored. On the following day he could move his legs and seemed greatly improved. The left knee jerk was absent. A loud to-and-fro murmur was heard over the base of the heart. The radial, carotid and femoral pulsations were bounding. He had a little fever and raised some blood-tinged sputum. The electrocardiogram was regarded as consistent with pericarditis. X-ray study of the chest showed a tortuous aorta and slight pleural effusion on the left. The blood Kahn test was negative. None of the several doctors who saw the patient thought of dissecting aneurysm. On the fourth day he died suddenly. Autopsy revealed a dissecting aneurysm beginning just beyond the aortic valves and extending down into the iliac vessels. A terminal rupture into the pericardial sac had occurred.

*This patient was seen at Veterans Administration Medical Teaching Group Hospital, Memphis, Tennessee, in January, 1950.

This case demonstrates that abrupt onset is more characteristic than pain. Numerous tentative diagnoses were made, including apoplexy of the spinal cord, hysteria, syphilitic heart disease, rheumatic heart disease, pericarditis, pleuritis and pulmonary embolism. If dissecting aneurysm had been considered, the correct diagnosis would have been obvious. No other diagnosis could adequately explain the loss of consciousness, transient paraplegia, aortic insufficiency, "pericarditis," pleural fluid and sudden death.

Diagnostic Approach

If dissecting aneurysm is thought of in every condition with abrupt onset that is not readily diagnosed as something else, it will rarely be missed. A precise description of the pain and its radiation is most helpful. Once the diagnosis is suspected, careful bedside examination usually reveals supporting evidence. The electrocardiograms will not be characteristic of an acute myocardial infarction but will probably be abnormal. X-ray studies initially are rarely diagnostic, but serial films may be of great value. Failure to demonstrate free peritoneal gas helps to exclude perforated peptic ulcer. The patient should be closely observed subsequently for murmurs, change in pulsations and the many other signs and symptoms that occur. The varied nature of these subtle manifestations (as in polyarteritis nodosa) characterizes the disorder. If death does not occur the diagnosis should not be dismissed completely, for many patients recover from the acute episode. Further observation of these patients will show a high incidence of subsequent dissection.

Treatment

The treatment of dissecting aneurysm is expectan and symptomatic. Complete and prolonged rest appears logical. The patient should probably be kept at rest for at least six weeks, but statistics are not available to substantiate or refute this estimated interval. Cellophane wrapping of the aorta has been performed, with survival of the patient[38]; however, no surgical therapy has yet been proved to be of value. Recent advances in vascular surgery make one hesitate to dismiss the possibility of successful surgical treatment. Anticoagulants are illogical. Drugs designed to lower blood pressure may be of some benefit if hypertension persists, but caution should be exercised if renal function is poor; indiscreet tampering with the blood pressure is dangerous.

Summary and Conclusions

The frequency of dissecting aneurysm is re-emphasized.

The diagnosis should be made during life in the majority of cases.

The family doctor, who sees most of the cases initially, is generally not well informed on the subject. Dissecting aneurysm will rarely be missed if it is considered in every catastrophic condition characterized by abrupt onset and not readily diagnosed as something else.

Bedside study of the patient yields the essential diagnostic data, whereas laboratory studies play a secondary role.

Hyperbilirubinemia may have a high incidence and should be further studied.

A "splitting" of the sound heard over the brachial artery while the pressure was being determined was observed in 1 case.

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METHOXAMINE HYDROCHLORIDE IN THE TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA*

Report of Three Cases

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Recent reports[1,2] in the literature have suggested that methoxamine (beta-[2.5-dimethoxyphenyl] beta-hydroxyisopropylamine) chloride,¶ a synthetic amine, is effective in terminating attacks of supraventricular tachycardia. To corroborate these observations, 3 cases are added to the 4 already reported. These 3 cases are of particular interest because continuous electrocardiograms were taken during the course of the attack during the administration of methoxamine hydrochloride. The electrocardiograms demonstrate a dramatic reversion of the paroxysmal to the normal rhythm in a matter of seconds. No attempt is made in this paper to compare the value of methoxamine hydrochloride with that of other established methods of treatment for this arrhythmia.

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Case Reports

Case 1. On September 6, 1953, A. T., a 50-year-old fireman, was admitted to the emergency room with a chief complaint of "rapid heart beat," which had begun 8 hours previously and, unlike several earlier attacks, he had not been able to terminate by holding his breath or pressing his hands on his abdomen. He felt profoundly weak and was perspiring profusely.

The past history was not remarkable except for occasional bouts of paroxysmal tachycardia usually lasting 3 to 5 minutes and occurring once or twice a year for the past 25 years.

Physical examination revealed a well developed, well nourished, apprehensive man whose skin was cold and clammy. The head, neck and abdomen were normal. The lungs were clear to percussion and auscultation. The heart was not apparently enlarged to percussion. The pulse rate was 230 beats per minute, regular and of poor quality. The blood pressure was 110/90. The remainder of the physical examination was negative.

An electrocardiogram revealed paroxysmal atrial tachycardia with a rate of 230 beats per minute. Attempts to revert the rate to normal by increased ocular pressure, the Valsalva procedure and carotid-sinus pressure were unsuccessful.

A few moments later, with the electrocardiograph running, the patient was given 10 mg. of methoxamine hydrochloride intravenously and 30 seconds later, after no change in the heart rate, another 10 mg. intravenously. Reversion to regular sinus rhythm occurred 53 seconds from the time of initial injection (Fig. 1). Immediately after reversion the patient became agitated, apprehensive, nauseated and fearful that "something was going to happen." These subjective sensations were fleeting, however, disappearing in a few seconds. The blood pressure rose to 140/90 4 or 5 minutes after the methoxamine hydrochloride and stabilized at 115/70 in about 60 minutes. An electrocardiogram 12 hours later was within normal limits. The sedimentation rate was 1 mm. per hour (Westergren); the basal metabolic rate was +3 per cent, and radioactive iodine uptake was 32 per cent (normal); the total cholesterol was 179 mg. per 100 cc. (normal). The remainder of the hospital course was uneventful.

The patient remained asymptomatic and was discharged on the 4th hospital day. In a follow-up report he stated that he was well and had no further attacks.

Case 2. On October 4, 1953, A. L., a 45-year-old woman, was admitted to the emergency room in a state of shock. Six months previously she had been hospitalized because of a bout of hematemesis but had left against advice before an adequate work-up could be accomplished. It was believed at that time that the illness was related to a gastrojejunostomy performed in 1941 for a duodenal ulcer. Four days before admission she had melena, which lasted for 2 days. There was no associated nausea, vomiting, hematemesis or abdominal pain. One hour before admission, on going outside from an overheated dwelling, she suddenly experienced syncope and was rushed to the hospital by ambulance.

Physical examination revealed a moderately obese woman whose skin was pallid and cool. Her sensorium was somewhat clouded. The pulse was thready and extremely rapid. Respirations were 26 per minute, and the blood pressure 90/60. The cardiac rate was excessively high by auscultation, and an electrocardiogram revealed paroxysmal atrial tachycardia, with a rate of approximately 300 beats per minute. There was no response to carotid-sinus or ocular pressure. With the electrocardiograph running, 10 mg. of methoxamine hydrochloride was injected rapidly into the right antecubital vein. The rate reverted in 35 seconds to a sinus tachycardia of 120 beats per minute (Fig. 2). The blood pressure immediately after reversion was 150/90. Two minutes later it was 110/70, at which it was stabilized. The patient promptly became lucid.

Figure 1. *Electrocardiogram (Lead 2) in Case 1. Arrow shows reversion to regular sinus rhythm thirty seconds after the intravenous administration of methoxamine.*

Case 3. On November 4, 1953, E. L., a 28-year-old female factory worker, was admitted to the emergency room with the complaints of rapid heart action and moderate substernal distress of approximately 1½ hours' duration.

The past history was irrelevant except for occasional transient cardiac "palpitations."

Physical examination revealed a well developed, asthenic woman, who was alert, co-operative and quite apprehensive. The cardiac rate was 220 beats per minute. The blood pressure was 110/80.

Figure 2. *Electrocardiogram (Lead 2) in Case 2. Arrow shows reversion to sinus tachycardia thirty-five seconds after the intravenous administration of methoxamine.*

An electrocardiogram showed a supraventricular tachycardia; 5 mg. of methoxamine hydrochloride was injected intravenously. Reversion to regular sinus rhythm, which began 50 seconds later, was complete in 1½ minutes (Fig. 3 and 4). During reversion there was a period of approximately 40 seconds of what appeared to be atrial fibrillation. The patient complained of nausea during but was subjectively well after the reversion.

She was admitted to the hospital for a 24-hour observation period. X-ray films of the chest, studies of the blood and urine, a repeat electrocardiogram on the following morning and a determination of the basal metabolic rate were within normal limits.

Discussion

These 3 cases clearly demonstrate that methoxamine hydrochloride, when administered intravenously, can promptly end an episode of supraventricular tachycardia. In Case 1 the attack, which was of about eight hours' duration, occurred in a patient subject to minor attacks over a twenty-five-year period. Although the blood pressure during the tachycardia was slightly lower than the normal level the attack was not complicated by profound shock,[3] nor was there any evidence of underlying cardiac disease. The attack was promptly terminated fifty-three seconds after the administration of two 10-mg. doses of methoxamine hydrochloride intravenously. During the reversion period the patient complained of weakness and nausea — a frequent occurrence during the transitional phase, even when the reversion occurs spontaneously. Electrocardiograms showed, during reversion, a momentary asystole, which apparently represents the interval required for the sinus node to initiate a normal sinus rhythm.[4] A similar period was demonstrated in the electrocardiograms in Cases 2 and 3, which revealed the tachycardia, the time of injection of the methoxamine hydrochloride and the reversion to normal rhythm after this brief period of asystole (Fig. 2, 3 and 4).

Figure 3. *Electrocardiogram (Lead 2) in Case 3. Arrow shows beginning reversion to sinus rhythm.*

Figure 4. *Further Tracing (Lead 2) in Case 3, Showing Complete Reversion to Regular Sinus Rhythm.*

The mechanism of the action of methoxamine hydrochloride as described in other papers[2,5] is said to be vagal stimulation. This is thought to be initiated by an increase in blood pressure acting on carotid-sinus and other pressor receptors. Recordings of blood pressures in these cases revealed a lowered level initially in Cases 1 and 2, and a normal blood level in Case 3. In all cases the blood pressure was elevated shortly after methoxamine hydrochloride and stabilized at a normal level a few moments later. In all cases ventricular extrasystoles occurred at the onset of the reversion, being followed in Case 3 by a brief period of what appeared to be atrial fibrillation (Fig. 1, 2, 3 and 4). After normal rhythm had been established no extrasystoles were noted on the electrocardiograms, and this tends to confirm the statement that methoxamine hydrochloride does not cause cardiac irritability as some of the other pressor amines do.[5,6]

Summary

Three cases of paroxysmal supraventricular tachycardia treated with intravenous injections of methoxamine hydrochloride are reported. In contrast to the previously reported cases in the literature 1 of these patients was not in vascular shock when treatment was instituted.

By the use of continuous electrocardiograms during the attack and treatment it is demonstrated that intravenous administration of methoxamine hydrochloride can terminate this arrhythmia in a matter of seconds.

No analysis of the comparative effectiveness of the drug is made, but it is suggested that further study may prove methoxamine hydrochloride to be of value as another therapeutic agent in this condition.

Since this article was submitted for publication, 3 additional patients have been treated with methoxamine intravenously, reversion occurring promptly in a matter of seconds. No prolonged period of asystole has as yet been experienced.

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MEDIASTINAL EMPHYSEMA COMPLICATING MYOCARDIAL INFARCTION*

Report of a Case

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SEVERAL recent papers have adequately described the clinical features of mediastinal emphysema. Most reports have incorporated the adjective "spontaneous." Further study suggests that precipitating factors were involved in most, if not all, cases and that the term "spontaneous" may therefore not be applicable.[1] Aisner and Franco[2] point out that it is important to seek out circumstances precipitating or predisposing to the given episode. When an injury has occurred it is obvious that the origin of the emphysema is traumatic. On the other hand, the factor may have been missed because of its apparent triviality, or it may have been forgotten and its causal relation unnoticed owing to the interval between its occurrence and the onset of symptoms. Such an occasion might be a short period of forceful straining or severe cough.

Other possible causes are acute infectious diseases such as influenza, pertussis, tuberculosis, aspiration of a foreign body, bronchial asthma, pulmonary neoplasm, positive-pressure-inhalation therapy, resuscitation by pulmotor, blowing of glass and playing of wind instruments. A combination of these factors may also be found.[3]

Mediastinal emphysema is the result of a change in the pressure relation between intra-alveolar air and pulmonary intravascular blood caused by one or more of the conditions mentioned above. Any increase in the intra-alveolar air or decrease in the intravascular blood, according to Macklin and Macklin,[3] causes an extravasation of air into the perivascular sheaths (interstitial emphysema). This air tends to flow toward and accumulate in the mediastinum as long as the pressure gradient persists. It may then escape into the pleural or peritoneal cavities or the subcutaneous or retroperitoneal tissues.

In the case reported below, mediastinal emphysema was precipitated by an attack of acute failure of the left ventricle with severe pulmonary edema that followed acute myocardial infarction. Like any syndrome with chest pain as the initial complaint, mediastinal emphysema may be mistaken for myocardial infarction and must be distinguished from it.[4] In the present case, however, there is valid evidence of the presence of both. I believe that this is the first report of mediastinal emphysema complicating recovery from acute myocardial infarction.

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CASE REPORT

A 78-year-old man was admitted to the hospital on May 4, 1953, after an attack of acute pulmonary edema on the preceding afternoon. For about 10 years he had had occasional episodes of substernal oppression on exertion, particularly if the exertion occurred after eating. There had been no signs of congestive cardiac failure although he had a chronic cough. A week before admission an attack of substernal pain that was unusually severe occurred after a meal. The pain radiated into the neck and down both arms. He was dyspneic but was able to move. His family noted that his complexion was ashen. He was treated at home. He became more comfortable so that by the 6th day he undertook to bathe himself. One hour later he became severely dyspneic; his breathing was loud and stertorous, and his responses dulled. Emergency measures were effective in alleviating the acute pulmonary edema, and he was removed to the hospital.

Physical examination revealed a man who appeared quite ill. He was orthopneic, with moderate cyanosis. He responded to questioning in a low and halting voice. The fundi showed Grade 2 hypertensive arteriosclerotic changes. The ears, nose and throat were normal. The teeth were in fair condition. The neck veins were not distended. The maximal point of the apical impulse was palpable in the 5th left intercostal space, 12 cm. from the midsternal line. The heart sounds were distant, and no murmurs or other adventitious sounds were heard. The percussion note over the lung fields was dull, and numerous fine and coarse moist rales were heard on both sides posteriorly. The abdomen was obese and soft. No organs or masses were palpable. There was no peripheral edema. The palpable arteries were firm and tortuous. Neurologic examination was negative except for tremors of the tongue and hands.

The pulse rate was 80 per minute and the rhythm regular. The blood pressure was 110/75. Respirations were regular at a rate of 36 per minute.

Urinalysis disclosed a pH of 5.0, with a specific gravity of 1.020 and a ++ test for albumin and a negative test for sugar; the sediment contained occasional leukocytes and bacteria. Examination of the blood showed a red-cell count of 5,340,000, with a hemoglobin of 15.0 gm. per 100 cc., and a white-cell count of 19,850, with 90 per cent neutrophils and 10 per cent lymphocytes. The blood urea nitrogen was 39 mg. per 100 cc.

By the 3d hospital day, the patient's color had improved, and dyspnea was diminished. He complained only of extreme fatigue. The blood pressure was still low (110/70). Rales could still be heard at both bases, but a soft, blowing, systolic murmur was detected at the cardiac apex for the first time.

During the night of the 3d day, he again became cyanotic and complained of dysphagia. It was at this time that crepitant swelling of the neck and supraclavicular areas was noted. The heart sounds were again distant; the left hemithorax was hyper-resonant on percussion, and the breath sounds were diminished on that side.

Subcutaneous emphysema spread upward during the next 3 days to involve the cheeks and eyelids. The respiratory difficulty decreased and, by the 10th hospital day, had completely receded.

On the 8th hospital day the blood urea nitrogen had diminished to 17 mg. per 100 cc., and the white-cell count to 10,200, with 74 per cent neutrophils, 2 per cent stab forms and 24 per cent lymphocytes. The sedimentation rate was 33 mm. per hour (Wintrobe method).

A bedside film of the chest on the 4th day after admission, when subcutaneous emphysema first became apparent,

was interpreted as demonstrating pulmonary edema, subcutaneous emphysema and possibly mediastinal emphysema.

Electrocardiograms (Fig. 1) were compatible with the diagnosis of acute posterior myocardial infarction superimposed on previous myocardial damage.

The patient continued to improve in the hospital. The myocardial lesion stabilized and he was discharged 37 days after admission on digitalis, diuretics and a low-sodium diet. No particular therapy had been given for the pneumomediastinum.

tion of the area of cardiac dullness demonstrated. There were physical signs of pneumothorax on the left, however—hyper-resonance and diminished breath sounds. The patient's critical condition precluded adequate roentgenographic demonstration of air in the mediastinum.

Subcutaneous emphysema, particularly of the neck and supraclavicular areas, is considered an important

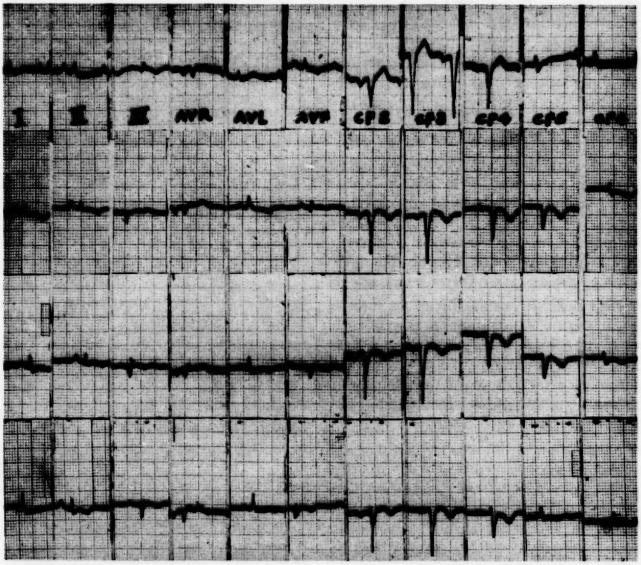

FIGURE 1. *Electrocardiogram in a Case of Mediastinal Emphysema Occurring after Myocardial Infarction.*

DISCUSSION

Most descriptions of mediastinal emphysema stress the paucity of constitutional symptoms in this condition,[2] which, in fact, is distinguished from myocardial infarction by the absence of fever, leukocytosis, increased sedimentation rate and electrocardiographic changes. Electrocardiograms, though changes occur in 25 per cent of cases of mediastinal emphysema, have demonstrated no characteristic pattern and have returned to normal within seven to fourteen days.[2]

In the case presented above, attention was drawn to the mediastinum by the development of subcutaneous emphysema. If this had not appeared, the secondary relapse might have been attributed to progression of the primary cardiac difficulty. Mediastinal crepitation (Hamman's sign) was not elicited, nor was diminusign of mediastinal emphysema, in the absence of wounds of the chest wall communicating with the lung or of trauma to the buccal or nasal cavity.[5] Laënnec[6] pointed out its diagnostic significance. Ballon and Francis[7] were able to show experimentally that air traveled into the subcutaneous tissues of the neck from the mediastinum by way of the deep fasciae and perivascular areolar tissue. Hamman[8] regarded the appearance of air in the subcutaneous tissues of the neck as diagnostic. The air need not be present in the upper part of the body, but may escape from the mediastinum, although less frequently, around the aorta and esophagus, through the diaphragm into the retroperitoneal area, the lower abdomen and thighs, and into the pleural cavities.[5]

The sequence of events in this case conforms to the pathogenesis of pneumomediastinum described by the Macklins.[3] The patient suffered a typical attack of coronary occlusion under circumstances compatible with such an episode. After a week of improvement he was confident in his ability to undertake an exertion that proved sufficient to precipitate acute pulmonary edema. The severe cough associated with the acute heart failure set into motion the mechanisms shown to induce mediastinal emphysema. Increased intra-alveolar pressure from cough caused extravasation of air into the perivascular sheaths (interstitial pulmonary emphysema). Accumulation of air and build-up of pressure forced the air toward and into the mediastinum, whence it escaped into the subcutaneous tissues of the supraclavicular areas, neck and face.

Summary

A case of mediastinal emphysema that followed myocardial infarction is reported. The emphysema may have been precipitated by cough associated with acute failure of the left ventricle.

The pathogenesis of mediastinal emphysema is briefly reviewed in relation to its occurrence in this case.

The significance of subcutaneous emphysema as a sign of mediastinal emphysema is discussed.

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SPECIAL ARTICLE

THE IMPACT OF DISEASE ON AMERICAN HISTORY

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ALTHOUGH there are medical histories dealing with America as well as the rest of the world medical histories, for the most part, are drab accounts of scientific discoveries, dreary biographic sketches of obscure or eponymous physicians or descriptions of epidemics as they affected the course of medical knowledge. None of them deal with the over-all effect of disease on the history of this nation.

A useful premise at this point is that before the white man invaded the North American continent it was a healthful place to live in. There is a good deal of evidence to support this claim. There were probably only about 2,000,000 native inhabitants in what is now the United States, but the population was limited much more by the available food supply than by decimation from disease. The population of the Caribbean Islands and Mexico was much denser, but in all these areas the earliest explorers such as Las Casas, Oviedo and their contemporaries invariably described the people as healthy and the land as a paradise. An even more potent argument that epidemic disease probably did not exist among the natives was the fact, soon to become obvious, that they had almost no racial or natural immunity to the diseases imported from Europe.

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Colonization

The factors contributing to the success of the early explorers and colonists in establishing and maintaining a beachhead and at long last in conquering the continent have been variously described. Without question they were men—and women—of courage and resourcefulness. Their motives ran all the way from deep religious fervor to utter greed. Some wanted gold, some wanted land, and some wanted position and power. Some wanted to convert the Indians to Christianity, and others wanted to force them into slavery. The Europeans had several advantages on their side. They understood military principles—the concept of command and leadership. They had powerful motives. Within their own national groups, whether Spanish, French or English, there were no language barriers, and so in that sense communication was simplified. They had supremacy on the waterways because of their naval background and equipment, and man for man, of course, they had overwhelming superiority in fire power—they had guns.

Effect of Disease

On the other hand they had several serious disadvantages. They were greatly outnumbered. They were battling a race that was fighting on its own ground and, in many cases, was not lacking in courage. Most important of all they were forced to maintain a supply line so extended and so tenuous that it seems incredible that they succeeded. The reason for their success is another premise, which has been overlooked by many historians: the Europeans were able to conquer America, not by their military genius, or their administrative ability, or their religious motivations, or their ambition and avarice, but by waging unpremeditated and unrecognized biologic warfare.

Obviously, such a statement demands proof. The proof is in the record. When Columbus discovered Hispaniola, that island paradise had an estimated population of 300,000 natives. Within half a century the Tainos had been practically exterminated by slaughter, starvation and "so many diseases, especially certain pestilential small-pox which prevails generally in all the island, that in a short time the Indians will be ended." So wrote Oviedo[1] in 1548.

The military problem that faced Cortes in 1519 when he set out to conquer Mexico would stagger a modern tactician. His enemy were not savages; the Aztecs were brave and intelligent and were fighting on their native soil. Cortes had 500 men, 11 ships, 32 crossbowmen, 13 musketeers and 16 horses. With this force he conquered a kingdom and established a government that endured for three centuries. And of the defeated, de Herrera[2] wrote, "There used to be a great number of Indians, but by reason of many diseases, and pestilences which they usually have in the province, they diminished greatly, because being sick with measles, small-pox, catarrhs, bloody flux and great fevers they bathe in the rivers without waiting for the diseases to subside, and so they die."

In Canada the French priests again and again deplored the fact that hardly had they succeeded in converting the aborigines to Christianity and persuaded them to go to church when they were afflicted with disease and died in great numbers. In the *Jesuit Relations* of the time are wistful entries such as the following[3]:

> Hardly had they [the Indians] left Tadoussac—where they had listened with love to the Christian truths and presented their children for baptism—when death fell upon those little innocents, and disease upon a great part of their parents. There is no human eloquence which can persuade a people to embrace a Religion which seems to have for companions only pestilence, war and famine.

There is also plenty of evidence that a similar fate attended the Indians in English America. For several years before the pilgrims landed at Plymouth there had been explorations and fishing expeditions along the New England coast and even abortive attempts at colonization, particularly on Monhegan Island. Again, the result, as far as the Indians were concerned, was disease. Samoset, who had learned some English from these explorers, told Governor Bradford of a terrible plague that had struck the area about 1617, killing off all the inhabitants of whole villages. It has frequently been assumed that this epidemic was smallpox, but there is reason to think it was not. What it may have been is not known. The Pilgrims assumed that God smote the Indians to make room for them, a rationalization that at this date seems a trifle smug.

After the Plymouth Colony had been established smallpox epidemics were recognized among the Indians. In 1631 a difference of opinion developed between the new Americans and the old that was settled, according to Increase Mather,[4] as follows:

> About the same time the Indians began to be quarrelsome touching the Bounds of the land which they had sold to the English; but God ended the controversy by sending the small-pox amongst the Indians at Saugust, who were before that time exceeding numerous. Whole towns of them were swept away, in some of them not so much as one Soul escaping the Destruction.

It would be entirely possible but completely pointless to produce a mass of further evidence to prove that the continent was largely conquered by disease. Smallpox, pneumonia, diphtheria, tuberculosis and similar infections killed far more Indians than swords or rifles ever did, but it would be utterly inaccurate to imply that disease held no terror for the invader as well as for the native. Disease, for example, determined that the first settlement of the Pilgrims in America should be in Massachusetts. In 1618 Francis Blackwell, a Pilgrim leader, set out from Amsterdam for Virginia with 180 persons crowded on one small vessel. By the time Virginia was reached 130 had died, including both Blackwell and the captain of the ship. The survivors hastened to return to Europe with all possible speed. The principal reasons for the disaster were poor sanitation, crowding and insufficient water and the consequent enteric disorders. It is interesting to speculate how better planning on Blackwell's part might have altered the subsequent cultural and political history of the eastern seaboard.

There is ample evidence that the settlers had a hard time after they had arrived and established themselves. George Percy[5] left a firsthand account of the situation in Virginia during the first summer at Jamestown:

> Our men were destroyed with cruel disease, as swellings, flixes, burning fevers, and by wars, and some departed suddenly. But for the most part, they died of mere famine. . . . Our food was but a small can of barley sod in water to five men a day; our drink cold water taken out of the river, which was at flood very salt, at a low tide full of slime and filth, which was the destruction of many of our men. . . . If there were any conscience in men it would make their hearts bleed to hear the pitiful murmurings and outcries of our sick men, without relief every night and day for the space of six weeks; some departing

out of the world, many times three or four in a night, in the morning their bodies trailled out of their cabins like dogs to be buried.

Slavery

At this point one must consider an element in American history that had such far-reaching sociologic and political implications that its medical influences have been largely overlooked. As far as this country was concerned it all started in Jamestown in 1619. John Rolfe[8] wrote simply enough: "About the last of August came in a dutch man of Warre that sold us twenty Negars." The slave trade had begun.

Slaves had been introduced into Spanish America long before this. The Indians had made poor laborers, and as they died off or fled their conquerors, Negro slaves were imported in ever-increasing numbers to supplant them. The mortality among the blacks themselves was appalling. It has been estimated that 4 African natives were captured for every 1 that survived to serve a useful purpose in this hemisphere. There is little doubt that the introduction and wide dissemination of malaria, yellow fever, and hookworm into the New World were due to the slave trade. It is highly probable that leprosy and yaws and possible that amebiasis had the same source. The misery and death caused by the introduction of these diseases into the Western Hemisphere cannot even be estimated. In one respect, however, there can be no cavil: the relentless destruction of the Indians as a race and as a formidable opponent to the whites was made doubly certain and infinitely more rapid by the introduction to America of the diseases brought by the blacks.

Inoculation

For the first hundred years after the landing at Plymouth the Massachusetts colonists suffered from poor health and worse *physick*. Then conditions began to improve. Cotton Mather, who spent his leisure reading the *Philosophical Transactions of the Royal Society*, convinced Dr. Zabdiel Boylston that the Turks might have something good in their method of inoculating variolous material into healthy but susceptible persons when smallpox was rampant. Boylston, with an exhibition of courage that must always command respect, staked his professional reputation, his personal safety and the life of his son on the gamble, with the result that several hundred Bostonians were inoculated against smallpox at a time when not a soul in western Europe had ever heard of variolation. Mather and Boylston had to engage a large group of the clergy as well as many physicians in a bitter battle, but the results were convincing, and by the time the next major epidemic struck Massachusetts, variolation had become comparatively fashionable.

Smallpox had many unexpected effects on colonial life in New England. A sharp outbreak occurred in Boston during the winter of 1763-64 and so frightened the General Court that that august body scrambled over to Cambridge and held its sessions in the college buildings until the festers in the city could heal. The rheumatic and chilblained legislators, however, required such roaring fires in the fireplaces of Harvard Hall that the whole building burned down, destroying the best collection of scientific apparatus and the finest library in the American colonies.

Revolutionary Period

Canadian Campaign

When the American Revolution began, the strategic importance of Canada was readily apparent to the Americans. By its possession they would not only deprive the British of an important base of supply but also deny them easy access to Lake Champlain and the Hudson River by way of the St. Lawrence. In the early autumn of 1775, 2000 militia under Montgomery set out from Crown Point for the attack on Canada and, despite rough travel over land and water, captured Montreal. Meanwhile 1100 picked troops under Benedict Arnold began their epic expedition up the Kennebec, across rugged terrain and then down the Chaudiere. Snow, log-filled streams, hunger and sickness beset them, but early in December, 675 of them had survived to meet Montgomery with his depleted forces on the St. Lawrence and together they besieged Quebec. On New Year's Eve they attacked the city but were repulsed; Montgomery was killed and Arnold wounded. In spite of this Arnold succeeded in maintaining a semblance of a siege, and reinforcements began to arrive. In March Congress made John Thomas a major general and sent him to Canada to take command.

Some day perhaps someone will write an article on doctors who served as line officers during the Revolutionary War. There were ten physicians, with April in their blood, who fought at Lexington and Concord. There were many more who later commanded regiments, brigades or divisions, and two with the rank of general, Joseph Warren and Hugh Mercer, who were killed in action. John Thomas, a physician of Kingston, abandoned his practice and was given a commission when the war broke out. He was a capable commander who had been instrumental in constructing the fortifications on Dorchester Heights, but the irony of the matter is that if he had been a better doctor he might have been a successful general. The most potent enemy that John Thomas had to face in Canada was not the British but smallpox. His troops had not been inoculated, presumably because he did not think there was time. It is possible, however, that he did not believe in the practice, because, apparently, he had never been inoculated himself. In his defense it might be pointed out that

immunization to smallpox in his day was a protracted procedure, which meant that military personnel would be incapacitated for several weeks. By the time Thomas arrived before Quebec the American camp was a shambles. The British made a sally, and the Americans fled, leaving their sick behind them. Thomas himself died of smallpox, and General Sullivan, who succeeded him, made one attempt to do battle and then retreated, leaving men dying in the woods and by the streams until the remnants of the Army staggered all the way to Crown Point at the southern end of Lake Champlain. "As fine an army as ever marched into Canada," wrote General Gates,[7] "has this year been entirely ruined by the small-pox."

It is idle to speculate whether eastern Canada would have been ceded to the United States if it had been in the possession of the Americans when the peace treaty was signed, but there is no question that it was not in American hands at that time because of the virus of variola.

Siege of Boston

During the winter of the siege, smallpox broke out in the city and made the situation thoroughly unpleasant for the British. Furthermore, the king's men suffered from scurvy. Red tape, supply problems and general confusion are not peculiar to modern armies, and much of the food intended for the redcoats in Boston landed at some distant port or was never shipped at all. It would be entirely inaccurate to imply that disease was a significant factor in forcing General Howe to evacuate the city on the celebrated March 17, because he had received orders to abandon the town months sooner, but there is little doubt that the condition of his troops added to his eagerness to quit the place when, in Howe's[8] own words, "I embarked with about 6,000 rank and file, fit for duty, and about 900 sick."

Middle Atlantic Campaign

The disaster in Canada was the outstanding virus victory of the first phase of the Revolution, but when the action moved into the middle colonies there were still many dreary days ahead for the rebels. The colonial troops found New York a very unhealthy place to be in and only partly because of His Majesty's forces. In September, 1776, there was an epidemic of typhus, and a third of the muster—8528 soldiers of the New York Army—were on sick report. Washington's withdrawal to New Jersey was not wholly due to the military genius of two brothers named Howe.

The Commander-in-Chief improved the time spent in winter quarters in Morristown by having his troops inoculated against smallpox, but from the point of view of hygiene there were few other examples of foresight or preparedness during this period.

The medical mobilization for the war was utterly inadequate both in personnel and in equipment, and completely uninspired. No one really had a reasonable idea of what was required, or how to achieve any semblance of basic needs. The results can be imagined. One report stated "between two and three hundred men are now here, returned unfit for duty, because there is not sulphur to cure them of the itch."[9] There was the celebrated brawl involving Drs. Morgan, Shippen and Benjamin Rush. In December, 1776, 7 of the rank and file were sick for every 10 who were present and fit for duty. The travail of Valley Forge is part of American folklore. It is hardly surprising that the colonial army, throughout most of this phase of the conflict, was an impotent military instrument.

Southern Campaign

During the third phase of the war, which was fought in the South, the Americans finally began to get a glimmer of a smile from Dame Fortune and less of the back of her hand. By now the colonial troops were hardened, their morale and equipment had improved, they usually had enough to eat and the sickness rate dropped. At the same time the law of averages began to catch up with the British. Previously, they could make tactical boners and ignore them; now, with strong American and strong French forces facing them, mistakes became costly. For the purposes of this discussion only one of these mistakes need be considered, and that is Yorktown.

Neither Cornwallis nor his superior in the war theater, Sir Henry Clinton, thought that British troops were accomplishing anything by scampering around Virginia maneuvering against Nathaniel Greene and Lafayette or, as Cornwallis wearily remarked, "marching about the country in quest of adventures."[10] But just as a transfer to New York was to be effected, orders came through to stay in Virginia and subdue the colony. In June, 1781, Cornwallis was directed to fortify Yorktown as a base for invading the southern colonies. The unhappy commander, who seems to have known how to designate a spade, called this "a defensive post which cannot have the smallest influence on the war in Carolina, and which only gives us some acres of unhealthy swamp, and is forever liable to become a prey to a foreign enemy with a temporary superiority at sea."[11] The general knew how to read his tea leaves.

It is perfectly logical for the military mind to insist on a conventional explanation for the surrender at Yorktown. Washington and Rochambeau had nearly 15,000 regular troops, and the French fleet was in the harbor. Cornwallis, with 8000 troops, was penned in by land and sea, and his supplies were failing. But it is not quite so simple as that. The British and Germans were battle-hardened professionals; Cornwallis was the best field general the British had on this continent, and Sir Henry Clinton was on his way

to the rescue with 25 ships of the line and 10 frigates carrying the best regiments of his New York army. But when Clinton arrived, Yorktown had fallen and Washington had taken 8000 prisoners. Eight thousand soldiers ably led, behind fortifications, can put up quite a fight when they know help is coming. But on that October day when Cornwallis lost an army, and a war, about 2000 of his troops were sick, in addition to his wounded. So Washington had another ally, besides the French, at Yorktown: one that rendered a fourth of his adversary ineffective. One can only guess at what the ally was, but since the weather had been warm and the defeated commander's rueful reference to "acres of unhealthy swamp" is available, it was probably malaria.

Louisiana Purchase

The nineteenth century began in a ferment of power politics, and the United States found itself unwillingly involved, especially along its western border. The Louisiana territory had been ceded to Spain as the result of French machinations at the time of the Peace of Paris in 1763. It was returned to France in 1800 by the secret treaty of San Ildefonso because Napoleon had dreams of a great colonial empire in the New World. As late as October, 1802, he had five battalions alerted to sail from Dunkirk to occupy New Orleans. Six months later he had sold the entire area to the United States for $15,000,000, thereby consummating the most gigantic real-estate transaction in history and doubling the size of the young republic at a stroke. It is true that Napoleon was an impulsive person, but such a sudden reversal of major policy seems strange. What happened between October and April? Historians usually offer the explanation that Napoleon was preparing to fight a war with England and needed the money. This sounds like a weak argument. Somehow, he always managed to finance his wars, and it seems doubtful if he would have sold a potential source of such wealth without trying other means to raise the cash. Another reason given is that he feared that he could not hold the territory against the power of the British fleet. This argument seems even more specious. The only place in the whole territory with water enough for the fleet to operate was New Orleans, and it is known that he had already planned the defenses there. Occasionally, however, a third explanation is offered—namely that Napoleon changed his mind about a colonial empire in America after the disaster in Haiti.

For three centuries, ever since the discovery of America, there had been a continuing struggle among the European nations for colonies in the Western Hemisphere, to be exploited for the benefit of the colonizing powers. When the French Revolution broke out there was a sizable French colonial empire in the West Indies, the most important segment of which was San Domingo—the western part of the island of Haiti, where there were rich plantations and heavy commerce with the homeland. In France, where there was no racial problem, the revolutionists proclaimed equality between whites and blacks, but the colonial planters refused to recognize the decree. The result was a bloody revolt, but eventually a very capable freed slave, Toussaint L'Ouverture, restored order, drove the English out of the island, occupied the Spanish portion and was made commander of the French forces in the colony.

By the time Napoleon came to power Toussaint believed that France, beset with European wars, would be in no position to deny independence to his people; he therefore declared himself governor for life, established a constitution for the island and boasted that he was the Bonaparte of the Antilles. In characteristic fashion Napoleon met the situation with force. In the spring of 1802 a strong contingent of French under the command of Leclerc, Napoleon's brother-in-law, landed in Haiti, assumed the offensive and defeated the blacks. And then disaster struck. On the wings of the Aedes mosquito was borne the force that the legions of the First Consul could not combat. Forty thousand men—soldiers, sailors, officers and civilians—died of yellow fever. In November Leclerc, the commanding general, died of the disease, and in January the news of the debacle reached Napoleon. A few weeks later he was telling Talleyrand, "I renounce Louisiana — the whole colony,"[12] and was offering two startled Americans, who had come over hoping to buy New Orleans, enough land to make all or part of 15 states. Napoleon had had his fill of the New World, where the swamps swallowed his generals and his legions. The Louisiana Purchase was accomplished through the efforts of Jefferson, Livingston, Monroe and the mosquito.

Old Northwest

After the War of 1812 the settlement of the Old Northwest began in earnest. This area is now Ohio, Illinois, Indiana, Michigan, and Wisconsin. In retrospect one tends to picture a group of robust pioneer men and women raising large and lusty families, exploring the Great Lakes and the rivers, subduing the forest, tilling the soil, hunting, fishing, and, during leisure moments, bagging an Indian, all in a spirit of good clean fun and in an atmosphere of abundant health and vitality. Nothing could be farther from the truth. The most lethal dangers the pioneers had to face were neither savages nor wild animals. They were typhoid, malaria, dysentery, malignant scarlet fever, pneumonia, erysipelas in epidemic form, spotted fever, or what would now be called meningococcal meningitis, and diphtheria.

One ailment peculiar to the territory and to the era was a condition known as the milk sickness or the trembles. Its etiology was obscure at the time, although the association with milk was apparent. It is

now realized that two weeds, white snakeroot and rayless goldenrod, contain a material that, when eaten by cattle, poisons the milk. The illness was violent, with muscle weakness, prostration, thirst and abdominal pains that were frequently followed by coma and death. It was of this miserable affliction that Nancy Hanks Lincoln died when her only living son was nine years old.

In 1832 there was a minor fracas with the Indians, and an overwhelming defeat for an expeditionary force of the United States Army. The Indian uprising was led by Black Hawk, who believed he could unite several tribes and gain the British as an ally to help him drive the Americans out of Illinois and Michigan. As it turned out, Black Hawk's ally came not from England but from India, and undoubtedly justice was on his side, but even so they were not enough.

In the first encounter Black Hawk and a handful of warriors routed the Illinois militia, and many of the settlers fled to Fort Dearborn. Because it was believed in Washington that a greater force than that locally available would be needed to quell the uprising, troops were ordered from New York and other eastern posts, under the command of General Winfield Scott, to take part in the campaign. On July 3 a lake steamer converted into a troopship set out from Buffalo for Detroit with the first contingent. On the following day one of the soldiers on board the vessel was suddenly taken violently ill and within seven hours was dead—of Asiatic cholera.

Asiatic cholera had been spreading westward from India since 1816. For years its progress had been slow, but by 1831 it was in western Europe and the British Isles and by the following year appeared in Quebec and Montreal and from there invaded Albany and New York. The arrival of the epidemic concurrently with the launching of a military expedition was fortuitous and devastating. As the troopship and the three that followed steamed from Buffalo toward Detroit the situation got out of hand. Two of the vessels were forced to land before the destination was reached. Disease, death, panic and desertion disrupted the expedition. At Detroit, where some of the troops were landed, the upper story of the capitol was converted into a hospital. When those able to travel were sent to Fort Dearborn they brought with them the disease, to disseminate it in Chicago and the West. In the week after the arrival of Scott's force at Chicago 200 were hospitalized and 58 died. Soldiers deserted, and civilians fled in terror; death was everywhere and struck with unnerving speed.

By the time Scott and a handful of officers arrived in the combat area to take command, the Illinois militia and some regulars who had left Fort Dearborn before the arrival of the infected troops had wiped out Black Hawk's braves at the battle of Bad Axe, and the conflict was over.

Civil War

The war that began when Fort Sumter was fired on in 1861 was the first of the modern wars. For one thing, the numbers involved were staggering. Neither Lincoln nor Davis had an officer, nor had there ever been one on the North American continent, who had commanded 30,000 men. By the time the struggle was over more than 2,000,000 had served on the two sides; a modern staff system had been evolved; wooden ships had become obsolete; William T. Sherman, to the eternal distaste of the Georgians, had originated the concept of total war; an efficient method of evacuating battle casualties had been developed; and it had been convincingly demonstrated that gallantry and tactical skill were no longer a match for industrial potential.

But all this took time. In the beginning the pattern was discouragingly familiar. The failure of McClellan to achieve a significant victory with the Army of the Potomac has usually been attributed to the personality of the general, but once more an aspect of the problem that has generally been overlooked should be mentioned. In its early days the Army of the Potomac was a sick army. There was a good reason for this. It always happens that whenever large groups of nonimmune people are brought together there will be outbreaks of infectious disease. Measles, which was a serious problem, was frequently fatal when followed by pneumonia. The camps around Washington were swampy, wet, undrained and unclean. Throughout the medical records of the Civil War are references to acute and chronic diarrhea and acute and chronic dysentery. Much of this, of course, was typhoid, and undoubtedly there was much of what would now be classified as salmonella infections and amebiasis; too frequently, however, the enteric disorders were caused by malnutrition.

Salt pork and hardtack comprised the cuisine during the early part of the war. For the Union armies from the beginning of the war until December 31, 1862, there were 1,661,602 on sick report for disease—482,764 for diarrhea and dysentery. It is small wonder that little of military consequence was accomplished during this period. In December, 1861, McClellan himself was sick and Lincoln, in one of his few despairing moments, cried out as follows:

> What shall I do? The people are impatient; Chase has no money and tells me he can raise no more; the General of the Army has typhoid fever. The bottom is out of the tub. What shall I do?[13]

The campaign on the Virginia Peninsula was McClellan's attempt to take Richmond by the back door and was probably poor strategy at best, but he succeeded in getting to a point where all that stood between him and the city were 5 miles of terrain—and Robert E. Lee. The Battle of the Seven Days that followed resulted in the retreat of the Federals to Harrison's Landing and an unsuccessful end to

the campaign; the combat had been fairly even, however, and the Army of the Potomac was still intact, so it is probable that if it had been commanded by a fighting general and supplied with a few wagonloads of lemons, it might have turned, crushed Lee, captured Richmond and ended the war in 1862. However, both factors—a general with androgens and a diet with vitamin C—were lacking. In two Massachusetts regiments alone there were more than 350 cases of scurvy. Dr. Jonathan Letterman[14] gave the following graphic description of the situation:

> This marching and fighting in such a region, in such weather, with lack of food, want of rest, great excitement, and the depression necessarily consequent upon it, could have no other effect than that of greatly increasing the numbers of sick after the army reached Harrison's Landing. Scurvy existed in the army when it reached this point. This disease is not to be dreaded merely for the numbers it sends upon the Reports of Sick: the evil goes much further, and causes which give rise to it undermine the strength, depress the spirits, take away the courage and elasticity of those who yet are not well. They do not feel sick, and yet their energy, their powers of endurance, and their willingness to undergo hardship, are in a great degree gone, and they know not why. In this way the fighting strength of the army was affected to a much greater degree than was indicated by the number of those who reported sick. . . . The data on which to base the precise percentage of sick and wounded could not then be obtained; but from the most careful estimate which I could make, the sickness amounted to at least twenty percent.

McClellan and McDowell and Burnside and Hooker all failed to elicit the fighting potential of what was to become a magnificent military force. Perhaps they were indecisive, incompetent, inept or afraid, as their critics have claimed; at least no physician would deny that they had their problems.

Little information is available regarding the medical experience of the Confederates during the war, but what there is indicates that they were as badly off as the Union forces, and perhaps worse. Lieutenant General Richard Taylor,[15] of the Confederate Army, has left a description of their lot:

> In camp our army experienced much suffering and loss of strength. Drawn almost exclusively from rural districts, where families lived isolated, the men were scourged with mumps, whooping-cough, and measles, diseases readily overcome by childhood in urban populations. Measles proved as virulent as small-pox or cholera. Sudden changes of temperature drove the eruption from the surface to the internal organs, and fevers, lung and typhoid, and dysenteries followed.

Spanish-American War

The Spanish-American War was almost a comic-opera affair. There was the villain, which was Spain, the clean-cut young hero, which was the United States, and the mistreated and helpless maiden, which was Cuba. There were the producers, Mr. William Randolph Hearst, of the New York *Journal,* and Mr. Joseph Pulitzer, of the New York *World.* There were the authors—literally dozens of them—exemplified by Richard Harding Davis, who swung his pen, and Sylvester Scovel, who swung his fist, at the Commanding General. There was the chorus, called the Rough Riders, who, in the news dispatches and in the mind of the public rode froth-nostrilled chargers into the gates of Hell, but whose equine equipage on the field of battle actually consisted of shanks' mare. There was the supporting cast—Dewey, who had one curtain call, Roosevelt and Wood, who went on to starring roles in other productions, and Sampson and Schley and Shafter, for whom this was the last time the lights would go up. But in spite of all this the whole thing did not quite make the grade as a comic opera. In the first place it really was not funny, in the second the dialogue was frequently tedious and invariably bitter, and finally there was some question about the dastardliness of the villain, the righteousness of the hero and the purity of the maiden in distress.

It was a strange war. The Spaniards were defeated before the fighting began, and the United States did not know its own strength—or, even worse, its appalling weaknesses. In March, 1898, Congress appropriated $50,000,000 for national defense and placed it at the disposal of President McKinley. Of this, the Medical Department, which was forbidden by law to accumulate reserve supplies in peacetime, was allotted $20,000 to squander as it might. This sort of financial preparation was for a campaign in which typhoid in the training camps and tropical diseases in the field would kill more than fourteen times as many men as enemy action.

Such is the fickleness of fame that most people, if they stopped to think about it at all, might assume that the Santiago campaign was under the direction of a couple of attractive personalities of field grade named Theodore Roosevelt and Leonard Wood. Actually there was a commanding general, and he is worth resurrecting from the oblivion that has engulfed him for half a century. His name was General William Rufus Shafter and he has the somewhat dubious distinction of having been, with little doubt, the largest general officer who ever commanded an American Army in the field: he weighed 310 pounds. Beneath this rather less than stern exterior, however, there beat a heart of courage, and over the excess of avoirdupois there presided a capable mind. Shafter's fat was not between his ears. Although he was hounded by journalists, hindered by politicians, hampered by the War Department and hamstrung by the Navy, he set forth from Tampa in the heat of June and landed at Daiquiri on the twenty-second with 17,000 men. A further statistic contains a significant commentary: he had with him 71 medical officers and 89 newspaper correspondents. He had taken his force 1500 miles by water; he landed on a hostile shore, and then proceeded to attack. He succeeded in driving the

enemy back from the shore but soon found himself in an extremely uncomfortable spot. The Spanish were entrenched high on a hill in the city of Santiago. From the point of view of terrain the enemy had the advantage; there were also formidable barbed-wire defenses, and the Spaniards outnumbered the Americans. Even more important was a factor well understood by Shafter — the yellow-fever season was at hand. He could retreat — because he still had his beachhead and naval superiority — but could he do anything else? There were alternatives — he could hurl his troops against the formidable defenses. But a fortified city is usually not attacked except by a superior force, or by one with much greater fire power or at least with the advantage of a considerable element of surprise. Shafter had none of these. He could lay siege to the city and starve the enemy out — but he knew that yellow fever would harm his own forces more than his acclimated enemy. There was one other alternative. It was one that probably would never have occurred to an Alexander, a Napoleon or a Marlborough and would have staggered Clausewitz. In short it would only have occurred to an American. In the face of overwhelming odds, Shafter demanded the surrender of his opponent — and got it. This is the sort of person that Americans usually adore. But there are no monuments to General Shafter, and the reason he never made the grade is simple. This was a newspaperman's war, and Shafter offended the press. He saw no reason why reporters should have priority when fighting men and firepower were needed. His failure to understand that this was a circulation rather than a military campaign made Shafter a nonentity for all time. He was buried by the Fourth Estate without a single drum. One of his clever subordinates, who realized that apples were meant to be polished, became president of the United States.

The surrender occurred on July 17, — less than a month after the landing, — and it was none too soon, for malaria and yellow fever soon reduced the victorious army to such a shambles that it had to withdraw in a hurry to ill prepared cantonments rapidly thrown up on the desolate stretches of Montauk Point.

The Panama Canal

The principal objective of the fourth voyage of Columbus in 1502 was to find a waterway from the Atlantic through the frustrating land barrier that he had previously discovered and supposed was blocking his way to the Indian Ocean. Other explorers had similar aims, so that many a keel scraped many a reef before it was finally realized that no passageway through the land mass existed besides the one Magellan poked into, too far south to be much good. This was in 1520, and in the next thirty years at least five surveys were made of possible canal routes through Panama or Nicaragua. Of these, three reported that the scheme was possible and practical. For the next three and a quarter centuries the project was "up for grabs." Spain, Great Britain, the United States, France, New Granada and Holland surveyed, dickered, plotted and jostled each other. During that time a stage route and later a railroad were built across the isthmus. Finally, in 1880, Ferdinand de Lesseps, who was primarily a promoter rather than an engineer, who had shoveled enough sand out of the way to connect the Mediterranean with the Red Sea and who had thereby become the foremost canal builder of his day, began to dig. But the poor man had three strikes on him. In the first place, and possibly least important, his engineering was bad, secondly, his financing was utterly corrupt, and finally, but not to be overlooked, was the fact that in the eight years of operation by la Compagnie Universelle du Canal Océanique there were 5527 deaths. As a matter of fact probably not more than a quarter of these were due to yellow fever — another quarter were due to malaria, and the remainder, excluding the accidental and intentional, were largely due to the diseases that accompany poor sanitation anywhere. A correspondent describes Colon as follows[16]:

> There are neither sewers nor street cleaners—toilets are quite unknown, all refuse is thrown into the swamps or onto rubbish heaps. Toads splash in the liquid muck . . . Rats infest the solid filth . . . snakes hunt both toads and rats; clouds of mosquitoes swarm into the houses. . . .

The combination of corruption and contagion brought la Compagnie down with a crash; the imported laborers rioted and fled, and the steam shovels and locomotives rotted and rusted in the jungle.

The next act in the drama is the familiar one. The first scene is in Cuba, and the important members of the cast are Carlos Finlay and Walter Reed, Carroll and Lazear, Agramonte and Gorgas, and heroic volunteers. Then the scene shifts to Panama, where Gorgas appears again, this time with Goethals. Here the dialogue is a bit stilted because there was no love lost between those two, but they got results. The introduction, in large quantities, of plumbing, pavement and pyrethrum made the centuries-old dream a reality, "and the mountains stood aside."

Discussion

A fascinating aspect of this subject that has not been included at all is the impact on history of the illness, or death from disease, of individuals. Here, one is even more in the realm of imponderables than previously. If Nathaniel Greene had not had a raging fever that prevented him from taking command at the battle of Long Island, would the result have

been different? Did the severe angina from which Robert E. Lee suffered during the last two years of the Civil War impair his military judgment? What were the effects on foreign and domestic policies of the incapacitating illness of Woodrow Wilson in the latter part of his second term? Would Franklin D. Roosevelt ever have returned to politics after his defeat in 1920 if it had not been for his absolute determination to conquer the crippling consequence of poliomyelitis? All these and many similar questions lie untouched. The effect of disease on national development has been only sketchily considered here. The subject warrants the compass of a volume and the devoted attention of a true scholar. When that scholar writes that book, it may be discovered that the generations in America have merely accomplished what the mosquitoes, flies, fleas, ticks, amebas, bacteria, rickettsias and viruses have been willing to permit.

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MEDICAL PROGRESS

THE COMMON COLD*

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THE accumulation of scientific information regarding the agent or agents that cause the common cold has been exceedingly slow. Many questions and problems confronting investigators twenty years ago remain with them today. What are the mechanisms of transmission of the disease from host to host? Is there a carrier state? Does the virus remain in the tissues continuously in a manner similar to the herpes simplex virus and produce infection only when the resistance of the host is altered, or is each infection an expression of a new contact with the agent? Does an immunity develop after an attack of the disease? Is the cold caused by a single agent, or are there many unrelated agents that produce similar nasal conditions? These are just a few of the questions. Although there has been much speculation about the answers, little experimental evidence has been advanced to support any of the ideas.

Virtually no advances were made in the methodology for studying the common cold during the time between the present day and the earliest investigation that proposed the concept of virus as the causative agent. Practical problems that were inherent in experimental studies undertaken by the early investigators also face the investigator of today. *There are no methods by which the virus may be studied in the laboratory, nor are there laboratory procedures that will establish the diagnosis of cold infection.* Because of this deficiency human beings must be the subjects of experiments, and this requirement severely limits the number and types of experiments that can be performed. This limitation, perhaps more than any other factor, is responsible for the slow accrual of information concerning the common cold.

This paper indicates briefly the extent of progress in understanding the nature of the common cold. It is not the purpose to present an exhaustive review of the literature, for the earlier work on this subject has been reviewed critically by Stuart,[1] Greenspan[2] and Hilding.[3] Because progress in this field has not been striking an additional review of the literature does not appear to be justified. However, the early pertinent investigations are mentioned, and the more recent publications are reviewed.

Definition

The common cold is defined as an acute epidemic respiratory disease characterized by mild coryzal symptoms of rhinorrhea, nasal obstruction and sneezing. The nasal discharge is usually copious and thin during the first two days of illness, after which it generally becomes more viscous and purulent. The

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disease is self limited. Symptoms may persist for two to more than fourteen days; however, the cold may abort after only one day. Fever, cough, sore throat or lacrimation may or may not be present. The common cold is of itself harmless, but bacterial invasion frequently follows the initial infection and it is these "secondary invaders" that may produce disorders of serious consequence such as sinusitis, otitis media, mastoiditis, meningitis, osteomyelitis, brain abscess and pneumonia.

It is unfortunate that the clinical description given above is not pathognomonic for the common cold but may also apply to other pathologic entities, including respiratory allergy, bacterial infections of the nose and sinuses and viral infections by influenza, primary atypical pneumonia and undifferentiated respiratory disease. A differential diagnosis may be exceedingly difficult, if not impossible, without information from the laboratory and from adequate case histories.[4,5]

Etiology

Kruse[6] first suggested that a filterable agent was responsible for colds. In his experiments intranasal inoculation of nasal secretions that had been obtained from patients with colds and rendered free of bacteria by filtration induced colds in human volunteers. Although several investigators failed to duplicate Kruse's observations, the work was amply confirmed in other laboratories. The most serious of these investigations was conducted by Dochez and his co-workers.[7] The virus that they isolated was readily transmitted to human volunteers and chimpanzees[7] and was established in vitro in cultures that contained embryonic chick tissues.[8] Virus that had been transferred from tissue culture to tissue culture for 88 passages proved to be infectious for human volunteers. With an in vitro method available for studying the virus it was anticipated that research would proceed more rapidly. However, this promise was not fulfilled, because cytologic alterations were not observed in the infected tissues. Once again the only method for determining the presence of virus was by the inoculation of human volunteers. In addition, it seems likely that other investigators experienced difficulty in duplicating Dochez's results, for little more was learned regarding the agent in the decade after their reports. According to Van Rooyen and Rhodes[9] the virus of Dochez "was not widely isolated," and virologists were therefore reluctant to accept this agent as the cause of most common colds.

In recent years two independent groups have undertaken an intensive investigation of minor respiratory infections. Dingle et al.,[10-12] first with the Commission on Acute Respiratory Illness during World War II and then later at Western Reserve University School of Medicine, re-examined the problem of virus in the etiology of upper respiratory infection. On several occasions they induced colds in human volunteers with filtrates of nasal secretions. Andrewes and his associates,[13] who are supported by the British Medical Research Council, have been conducting elaborate, well controlled experiments at Salisbury, England. In the course of many experiments, they had induced in human volunteers by 1949 an aggregate of 137 upper respiratory infections that were indistinguishable from the common cold.[13] On the basis of the results obtained by these two large investigations and by the earlier work, it seems reasonable to conclude that viruses can cause mild colds since nasal secretions that were rendered free of bacteria have repeatedly induced the disease in human beings under controlled experimental conditions.

The experimental infection and the agent that causes the infection have been characterized to some extent. Although the severity of the disease has varied from person to person, in general it appears that the experimental infections are milder than the naturally occurring ones.[10,13] The clinical features of the disease conform to the definition given above, in that the objective signs and symptoms were mostly referable to the nose. A clear discharge was observed early in the infection and was followed by a purulent one later in the course of the disease. Fever was generally absent, and a rough or scratchy throat was frequently observed.[13,14] The incubation period, — that is, the symptom-free period,—which occurred after the inoculation of infectious material and before the onset of symptoms, was reported to be between twenty-four and seventy-two hours; however, both shorter and longer periods occurred occasionally.[10,14] The experimental colds persisted for three to seven days. Colds that continued longer than seven days were rarely observed. In contrast, naturally occurring disease lasted longer in that symptoms frequently continued for about two weeks.[13,15]

In studying the course of experimentally induced colds, Andrewes[14] demonstrated that virus was present not only in the copious nasal discharge of the fully developed cold but also in nasal washings obtained during the incubation period. First, human volunteers were inoculated with cold virus. Then washings were obtained from the nose at various times after the inoculation. When symptoms began on the second or third day after inoculation nasal secretions were collected. Both the nasal washings and the nasal secretions were assayed for virus activity by tests in human volunteers. No virus was found in the nose after twelve hours, but at twenty-four hours after inoculation (which was considered at least twenty-four hours before the onset of symptoms) virus was present in quantities as potent as the nasal secretions obtained during the first two or three days after the onset of symptoms. Virus was also found in the nose as late as seven days after onset of symptoms. Of particular interest was the finding of virus in the nose before symptoms developed, for this indicated that virus had multiplied and the infection was established and con-

tagious, all in the absence of objective physical signs or symptoms of disease.

Properties of the Virus

Several laboratories have reported the isolation of an agent that produced colds in human volunteers. In the absence of serologic or laboratory methods for studying these viruses it was impossible to define such agents on the basis of antigenic criteria. Therefore, it was not known to what extent they were related, if at all. The following properties have been reported for such viruses.

Stability

The virus isolated by Dochez and his associates[7] could be stored for at least four months at dry-ice temperatures. Filtrates of nasal secretions appeared labile at icebox and higher temperatures. Such material proved inactive after two days' storage at 4°C.[7] Maintenance of filtrates under anaerobic conditions[16] or concentration of virus by vacuum distillation[8] preserved virus activity for longer periods of storage at 4°C. A few minutes' exposure to 56°C. destroyed its infectivity.[17] Their virus that was grown in tissue culture appeared more labile than the original one. Freezing destroyed its activity, but the activity could be preserved if gum acacia was added to the suspension of virus before freezing.[8] The viruses recently isolated appear more stable. The virus of Andrewes[14] remained active after storage for two years at −76°C., twenty-seven days at −10°C. and at least three days at refrigerator temperatures (no end point was determined). The virus resisted drying in the air to some extent. Nasal secretions that were dried in a handkerchief and were later freed from the handkerchief still produced colds in volunteers.[13] Virus employed by Feller and his associates[12] was frozen at temperatures of −76°C. and stored at −20°C. for over a year without loss of activity. Pollard, Dernehl and Caplovitz[18] reported the survival of cold virus after storage at −20°C. for one hundred and fifteen days.

Filterability and Size

Cold virus has been filtered through V, N and W Berkefeld candles,[7,19] Seitz E. K. pads[10,18,20] and collodion membranes.[14] Andrewes[14] filtered virus through a series of graded collodion membranes that differed in their average pore size. The results of this experiment indicated that the cold virus probably had a diameter of about 40 to 50 millimicrons, which would make this virus about half as large as the influenza virus and twice that of the poliomyelitis virus.

Host Range

The earlier work by the groups of Dochez[7] and Long[19] and the more recent work by the Commission on Acute Respiratory Diseases[10] and Andrewes[14] leave little doubt that under controlled experimental conditions a filterable agent can produce in human subjects symptoms that are similar to naturally acquired colds. Chimpanzees are probably the only animals besides man that are susceptible to cold virus. The early work of Dochez established this fact. Colds were produced in chimpanzees in 7 of 16 attempts, an attack rate of 44 per cent.[7] Andrewes[13] vainly attempted to establish colds in a variety of animals, including several species of monkeys. In 1953, according to a newspaper correspondent, Andrewes[21] was reported to have induced colds in chimpanzees. However, these experiments were discontinued because the chimpanzees usually contracted pneumonia as a complication secondary to the original cold infection. In addition the cost of these animals was prohibitive (£200, or approximately $560).

Kneeland, Mills and Dochez[22] reported the cultivation of the cold virus in embryonated eggs. Cold virus was dropped onto the chorioallantoic membrane. After an incubation period of two or three days the membranes were harvested and ground up in broth, and a portion of the suspension was inoculated into a second series of eggs. Material obtained from their third passage produced head colds in 2 volunteers. The employment of controls was not reported. In recent years three independent groups have reported the successful cultivation of cold virus in embryonated eggs.[23-25] Each group inoculated filtrates of nasal secretions into the allantoic cavity. After a suitable period of incubation allantoic fluid was harvested from eggs that were assumed to be infected, and an aliquot of the fluid was reinoculated into a second series of eggs. In this manner several blind passages were made. Topping and Atlas[23] reported that allantoic fluids from the fourth, sixth and seventh passage induced colds in human volunteers. The fifth-passage material of Ward and Proctor[24] and the twelfth-passage allantoic fluid of Pollard and Caplovitz[25] also proved infectious for human beings. On the other hand Andrewes,[13] who is an experienced investigator, has been unable to confirm these observations after experimentation on a large scale. The apparent discrepancy between the results in the United States and those in England may be an expression of differences in the respective viruses. The resolution of this problem must await the development of better methods for studying these viruses.

The early investigations of Dochez, Mills and Kneeland[8] and of Powell and Clowes[26] indicated that the virus of the common cold could be cultivated in suspended cell tissue cultures that contained minced, whole chick-embryo tissues. One strain of virus studied by the former group was transferred serially from tissue culture to tissue culture for more than eighty-eight passages. Fluid taken from the eighty-eighth passage produced cold infections in human beings. In similar experiments the twenty-seventh

passage material of Powell possessed viral activity. In the past few years Andrewes and his co-workers[13,27] have explored the technics of tissue culture as a possible method for the cultivation of cold virus. After many failures they finally reported the successful propagation of their virus in the roller-tube cultures that contained minced human embryonic lung.[27] Evidence was presented that the tenth serial passage produced colds in volunteers.

However, the methods were beset by technical difficulties. In the first place the virus lost its power to produce infections in human beings during the sequence of subculturing, and material obtained from passages subsequent to the tenth were innocuous for human volunteers. The virus obtained from cultures appeared to be less virulent than virus from nasal secretions. A discouragingly low attack rate of 10 per cent was reported. Thus, a total of only 13 infections out of 130 trials were recorded for cultured virus. Finally, the virus produced no obvious alteration in the cytology of the infected cells, and therefore the evaluation of virus activity still required volunteers. In view of the technical problems Andrewes et al.[27] stated that the tissue culture cannot yet be considered practical for study of the cold virus in the laboratory.

Pathology

There is a dearth of information regarding the cellular changes that occur during and after infection of the upper respiratory tract. The cold and other respiratory infections are generally benign and of short duration, and for this reason nasal tissue rarely reaches the pathology laboratory for histologic examination. Hilding[28] circumvented this limitation by accumulating 25 biopsy specimens from the inferior turbinates of patients with cold infections. He studied the cytology of these specimens, as well as material from 100 scrapings of the nasal mucosa. The results of this investigation demonstrated that the epithelium was denuded of ciliated cells during the first forty-eight hours after the onset of symptoms. Polymorphonuclear cells and macrophages were evident at twenty-four hours and thereafter were abundant, especially during the purulent stage of infection. After two weeks ciliated cells were regenerated, and the mucosa was repaired. The observations of Bryan and Bryan[29] provide indirect support for Hilding's investigation. Nasal secretions obtained from persons with acute upper respiratory infections were placed on glass slides, stained by a modification of Papanicolaou's method and examined under the microscope. By this means cellular inclusions were observed in the desquamated ciliated epithelial cells. The finding of inclusion bodies suggested to them the viral etiology of their infections. The possibility that the observed phenomenon was due to bacteria or to viruses other than the common cold was not investigated.

Studies in this laboratory demonstrated that ciliated cells are exceedingly numerous in the secretions of certain infections of the upper respiratory tract.[30] These cells were observed primarily during the first twenty-four hours after the onset of symptoms. Bacteria were virtually absent from these secretions, and influenza virus was not demonstrated either in the secretions or in throat washings from the same patient. The possibility that the desquamation of ciliated cells was caused by the cold virus has not been tested. However, in the absence of a history of allergy, organic nasal disease or a readily demonstrable infectious agent, the results suggested that these infections may be caused by the cold virus. In contrast, in other acute respiratory infections that were indistinguishable from the first group on clinical symptoms alone, bacteria were numerous in the secretions at the start of rhinorrhea. Ciliated cells were seen rarely, and inflammatory cells, which were abundant early in the infection, were repeatedly observed as long as the nasal symptoms persisted. Influenza virus was not detected in this group of infections. The data accumulated thus far, which are incomplete, suggested that the cellular response of the upper respiratory organ to bacterial invasion may be different from that to virus infection.

Infection of embryonated eggs[20,22] or of tissue cultures [8,27] by the cold virus has not produced gross or microscopical lesions in the affected tissues.

(To be concluded)

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MEDICAL INTELLIGENCE

MODIFIED KONDOLEON OPERATION FOR ELEPHANTOID LEGS

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ELEPHANTIASIS of the legs is a crippling disability, attempts at the surgical correction of which are often unsatisfactory. This paper, which is based on work done by me and my associates in Rajahmundry, in South India, describes an operation that may be of interest to surgeons in other parts of the world. The procedure, with the modifications indicated, does not require too much time and is not followed by complications. Skin grafts take well, and healing occurs in a surprisingly short time; patients are afebrile throughout the postoperative period.

TECHNIC

In 1874 Sappey observed that the deep fascia forms an impenetrable barrier for the exchange of lymph between the superficial and deep lymphatic systems in elephantoid states. Kondoleon confirmed clinically the observation that the tissue is superficial to deep fascia and that its abundant growth is due to the nourishment derived from the stagnated lymph.

Kondoleon's operation consists of excision of strips of deep fascia and subcutaneous tissue and closure of the wound. The slight reduction in the size of the legs and the poor cosmetic results made me completely modify the original Kondoleon procedure. This modified operation has afforded relief. The typical reduction in the size of the legs is shown in Figures 1 and 2.

Some authors have described total excision of elephantoid tissue, supplemented by skin grafting, but with no indication if the deep fascia is completely excised. This is important for in these cases the deep fascia is sclerosed and often calcified because of recurrent attacks of inflammation. The few normally existing apertures in the deep fascia are found to be completely occluded. The need for excising the elephantoid tissue along with the deep fascia to establish communication between the superficial and deep lymphatics with immediate skin grafting is emphasized.

Preoperative care of the patient includes elimination of focal and local sepsis. Nutritious food, liver extract, iron and components of the vitamin B complex are given to counteract undernutrition and anemia. A prophylactic dose of tetanus antitoxin is also given.

FIGURE 1. *Appearance of a Patient with Elephantiasis before and after Operation.*

The anesthetic of choice is 8 to 10 cc. of 1:1500 solution of dibucaine (Nupercaine) hydrochloride given by the spinal route. This reduces the blood pressure to the desired level to minimize bleeding from the excessive area from which the elephantoid tissue is to be excised. Soon after the anesthetic has been administered the limb is held up for about three

minutes as in operations for the removal of cartilage of the knee joint, and a tourniquet is applied over the midthigh region.

Large Thiersch graphs are then carved from the elephantoid growth by means of an ordinary straight

FIGURE 2. *Photograph of Another Patient, Showing the Appearance of the Elephantoid Leg before and after Operation.*

razor. As the skin is stretched over the elephantoid tissue, cutting of the skin grafts is very easy. The grafts are preserved in saline solution.

An incision is made around the posterior aspect of the leg at the proximal end of the gross lesion, and the veins are ligatured at each end to prevent bleeding while the elephantoid tissue below is excised. The patient is then turned on his back or the limb flexed and the incision extended anteriorly over the proximal end of the growth; the elephantoid tissue below is then shelled out with the deep fascia, exposing the muscles throughout. This is done conveniently through a vertical incision extending onto the dorsum of the foot and deep to the muscles. The procedure of shelling out the deep fascia along with the elephantoid tissue has the double advantage of less bleeding and shorter time for excision. The dissection on the posterior aspect of the limb is facilitated if one supports the limb on blocks, covered by sterile towels. The time taken for excision is about forty minutes. The tourniquet is released, and the bleeding points are ligated or controlled by hot packs and pressure.

The raw surface is then dusted with sulfonamide powder; penicillin solution, 100,000 units in 10 cc. of water, is instilled over the area. The area is then grafted with skin, which is kept spread by a stitch here and there as required.

The area is covered with large sheets of vaseline gauze; occlusion plaster is applied and is removed 10 to 12 days after the operation. The results are gratifying. Evenness in the limb is induced by elastic bandages over the grafted surface for a month.

General septicemia is not encountered in these cases, though antibiotics are not used as a routine postoperatively. Immediate skin grafting and pressure bandage and occlusion plaster ward off postoperative shock. Routine blood or plasma transfusions are unnecessary. There has been no mortality in these cases.

Histologic study of the excised tissue reveals perivascular infiltration of round and plasma cells with abundant increase of fibrous tissues and lymphangitis and endophlebitis.

The cases are being followed. Fissures on the dorsum of the foot discharging serous fluid, which were noticed in some cases, were successfully controlled by oral administration of components of the vitamin B complex and cod-liver-oil dressings.

Correction: The spelling of the drug "Pentylenetrazol" in the title and throughout the text of the article by Dr. John B. Andosca in the March 18 issue of the *Journal* should be corrected to "Pentylenetetrazol."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40161

PRESENTATION OF CASE

A forty-six-year-old man was transferred to this hospital with a diagnosis of "chronic renal disease."

He had been in good health until two months previously, when progressive weakness began. He had occasional bouts of nausea followed by the vomiting of watery material, but never of food or blood. He continued to work as a "floor boy" in a rubber factory. One and a half months before entry, after a bout of nausea and vomiting, he visited a physician, who said that he had "high blood pressure and anemia." The patient was given pills, and subsequently the stools became black. He had been unable to work since that time because of weakness. Symptoms became progressively more severe, and two weeks before admission, he was admitted to another hospital. At that time he appeared pale, lethargic and chronically ill. Positive physical findings included tachycardia (rate of 100), a Grade 2 systolic murmur heard both at the apex and in the aortic area, and a blood pressure of 160 systolic, 70 diastolic. The urine had a specific gravity of 1.007 and gave a + test for albumin; the sediment contained 5 to 8 red cells and 5 white cells per high-power field, but no casts. The blood hemoglobin was 7.5 gm. per 100 cc., and the white-cell count 18,500. The serum nonprotein nitrogen was 240 mg., the phosphorus 9.0 mg., and the calcium 6.5 mg. per 100 cc. The sodium was 132 milliequiv., the potassium 5 milliequiv., and the chloride 92 milliequiv. per liter. The carbon dioxide was 16 vol. per cent. The patient was treated with intravenous infusions of fluids, after which the nonprotein nitrogen fell to 142 mg. per 100 cc. During the next two weeks the clinical picture and laboratory findings remained about the same despite continuation of similar therapy in addition to a low-protein diet. He was transferred to this hospital.

There was no past history of rheumatic fever, chorea or "growing pains"; nor had he ever had hematuria or any other symptoms referable to the genitourinary tract. Fifteen years before admission he had had "quinsy sore throat." He had had a chronic discharge from the ears since childhood but without any hearing loss. During the present illness he had not had dizziness, headache, shortness of breath, ankle edema, puffiness of the eyelids or petechiae.

Physical examination showed a well developed, sleepy man, who appeared chronically ill. His breath had a uremic odor. The skin was dry and pale but without icterus or cyanosis; there were two small petechiae on the back. The lymph nodes were not enlarged. There was a small conjunctival hemorrhage and another on the posterior pharyngeal wall. There was a chronic, bilateral otitis media. Rales were heard over both lung bases, and there was a questionable pleural friction rub in the left axilla. The left border of the heart was at the midclavicular line; cardiac rhythm was normal. There was a Grade 3 systolic murmur at the left sternal border and base, and a Grade 2 diastolic blow at the lower end of the sternum. No diastolic rumble was heard at the apex; the aortic second sound was louder than the pulmonic. The liver edge was palpated 1 fingerbreadth below the costal margin and was nontender. No other abnormalities were noted in the abdomen, and there was no costovertebral-angle tenderness. The prostate was not enlarged. There was no peripheral edema, and neurologic examination was negative.

The temperature was 99°F., the pulse 85, and the respirations 25. The blood pressure was 140 systolic, 70 diastolic.

The urine was yellow, had a pH of 5.5 and a specific gravity of 1.008 and gave a ++ test for albumin; the sediment contained 10 to 20 white cells, 2 to 10 red cells and a few hyaline casts per high-power field. A urine culture grew out abundant colonies of *Escherichia coli* that were not sensitive to any of the usual antibiotics. Examination of the blood disclosed a hemoglobin of 7 gm. per 100 cc., and a white-cell count of 6800, with 79 per cent neutrophils, 17 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils. The red blood cells were normochromic and slightly microcytic. The blood Hinton test was negative. The serum nonprotein nitrogen was 145 mg., the total protein 5.5 gm., the albumin 2.9 gm., the globulin 2.6 gm., the calcium 7.2 mg., the phosphorus 5.5 mg., and the alkaline phosphatase 1.9 units per 100 cc.; the serum sodium was 127 milliequiv., the potassium 3.7 milliequiv., the chloride 87 milliequiv., and the carbon dioxide 20 milliequiv. per liter. The prothrombin time was 23 seconds (normal, 13 seconds). A stool specimen gave a +++ guaiac reaction.

A roentgenogram of the chest revealed some cardiac enlargement, probably chiefly of the left ventricle. The pulmonary vessels were engorged, and there was a small amount of fluid in both pleural spaces. A plain film of the abdomen did not show any visceral enlargement or stones. An electrocardiogram demonstrated changes of probable hypertrophy of the left ventricle.

In spite of intensive intravenous fluid and electrolyte therapy the clinical picture remained about the same. Improvement in the blood chemical findings was no more than temporary at any time. The prothrombin time was brought to normal with Hykinone, and the blood hemoglobin raised to 9.6 gm. per 100 cc. with multiple transfusions. A twenty-four-hour urine sodium was found to be 36 milliequiv. per liter, with a total output of 3 liters. An ear, nose and throat consultant found the mastoids and canals normal. There was a foul exudate deep in the canals bilaterally, and both drums were partially destroyed. On the ninth hospital day it was learned that multiple blood cultures taken shortly after admission had grown out "markedly pleomorphic, gram-positive cocci." The spleen was palpated by some observers but not by others; slight splenomegaly was confirmed by x-ray examination. On the twelfth hospital day a small, red, linear streak was noted under one fingernail. The organism found in the blood cultures proved difficult to grow even in broth, and antibiotic therapy was withheld to determine sensitivities and for additional blood cultures. Cultures of the ears grew out *Proteus vulgaris, Pseudomonas aeruginosa* and diphtheroids; beta-hemolytic and nonhemolytic streptococci were grown in the thioglycolate tube. Another urine culture showed abundant *Ps. aeruginosa* and also *Esch. coli* and beta-hemolytic and nonhemolytic streptococci. Throughout the hospital stay the temperature curve was irregular, ranging from normal to 100 and occasionally to 101 or 102°F. On the twenty-second hospital day the white-cell count was 31,000; the maximum temperature on this day was 101°F., and the pulse reached 120, later falling to 90. From the fifteenth to twenty-ninth hospital days intensive penicillin therapy was given, with doses up to 12,000,000 units daily in addition to 2 gm. daily of streptomycin. These did not seem to modify the course and chloromycetin was substituted. Pulmonary edema gradually developed, becoming severe on the twenty-eighth hospital day. Examination at this time showed marked respiratory distress. There was some deep pulsation of the neck veins, without much distention. There were many moist rales throughout both lungs, with some dcreased breath sounds laterally. Heart sounds were obscured by rales and rhonchi; a loud, Grade 3 to 4 systolic murmur was audible at the apex and base, and a questionable faint diastolic murmur to the left of the sternum. The spleen was not palpable; there was ++ peripheral edema. The patient was given digitoxin but continued to have pulmonary edema. A pericardial friction rub was heard, and this persisted. An electrocardiogram showed marked ST-segment and T-wave abnormalities, which were widespread and possibly due to a pericarditis. By the thirty-first hospital day the white-cell count had risen to 45,000; the temperature was 100°F., the pulse 120, and the respirations 26. He became weaker, had more difficulty breathing and died on the thirty-third hospital day.

Differential Diagnosis

Dr. Earle M. Chapman*: Perhaps we should look at the x-ray films.

Dr. Joseph Hanelin: In the chest films, which extend over a three-week period, initially there is evidence of cardiac enlargement, which appears to be predominantly of the left ventricle. There are engorgement of the pulmonary vessels and probably a minute amount of pleural fluid bilaterally. Interestingly enough, ten days later the engorgement and congestive changes in the lung have disappeared, and there is no longer any evidence of pleural effusion. At the last examination the heart is again enlarged, and there is evidence of extensive pulmonary congestion and bilateral pleural effusion. There is an area of more homogeneous density in the lower portion of the right side of the thorax that may largely be due to loculation of fluid although I cannot exclude a consolidative process in the right lower lobe.

The abdominal films are noncontributory. It is difficult to identify individual viscera because there is not much intra-abdominal fat. I cannot make out any calculi or abnormal masses. There is normal distribution of bowel gas.

Dr. Chapman: The kidney outlines are not particularly well shown.

Dr. Hanelin: No; that is primarily due to the lack of fat around these structures.

Dr. Chapman: The information I get from the radiologist is that the patient had cardiac enlargement chiefly in the region of the left ventricle, no evidence of calcification of the valves and no evidence of calcification or masses in the region of the kidneys.

Can you point out the splenomegaly?

Dr. Hanelin: I am not sure of splenomegaly: it is difficult to trace the splenic shadow.

Dr. Chapman: In summary it seems clear that when this man was admitted to the hospital the diagnosis of chronic renal disease was probably correct. I am not sure that an illness of two months' duration should be labeled as chronic; I think it might better have been called subacute. It seems, however, that the fundamental difficulty in this case was not renal disease but a form of subacute bacterial endocarditis — endocarditis of two or three months' duration

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(whether one calls it subacute or chronic in this time interval is an academic matter). To postulate the presence of subacute bacterial endocarditis I must assume some damage to a heart valve by rheumatic infection, perhaps early in youth, and also aortic valvulitis. The diagnosis of rheumatic heart disease is possible because of the diastolic murmur that indicates aortic regurgitation. A chronic infection had been present for years, with a suppurative discharge from both ears that could have served as the source of bacteria for the endocarditis that landed on the aortic valve. This in turn may have showered emboli to the kidneys, resulting in diminution of renal function and leading to death in uremia — this all seems like a logical sequence. I doubt if this was a primary renal disease; I prefer to look upon it as the typical embolic type of nephritis that comes from continued bacteremia.

The organisms were singularly resistant to both penicillin and streptomycin. I was surprised that the new antibiotic, polymyxin (Aerosporin), was not tried in this case because I have been led to believe from the literature that it has been particularly effective against organisms such as those cultured from the ear and also from the urine in the case under discussion.

One point that I shall comment on is the friction rub, which persisted until death. There was some discussion of this subject on medical rounds not long ago. A pericardial friction rub used to be considered a fatal sign, but we now know that a few patients with uremia have recovered even though a friction rub had appeared. The changes in the electrocardiogram fit in with the uremic type of pericarditis. The guaiac-positive stools suggest uremic colitis as well. One wonders if there was a myocardial infarction in the course of the final illness. I cannot make that diagnosis, but I must consider it in view of the electrocardiographic changes.

The history indicated that the patient was a worker in a rubber factory. He had a high white-cell count, which is consistent with bacteremia or bacterial endocarditis, but one wonders if he had some form of bone-marrow stimulation, with myeloid hyperplasia. The differential count suggests that the white blood cells were normal. We know that work in a rubber factory is hazardous and that one of the hazards is benzene. We do not have evidence that he had benzene poisoning, however. I do not think he had lead poisoning for I am not aware that one comes in contact with lead in a rubber factory.

In conclusion I have no other choice than the diagnoses that I have outlined. I do not know the type of the organism that was described as a pleomorphic gram-positive coccus. I should be interested to know if further bacteriologic studies identified it.

Dr. Lawrence Kunz: Dr. Louis L. Dienes became interested in this organism and made further studies of it. Perhaps Dr. Sharp, who is working in Dr. Dienes's laboratory, would like to comment on their findings.

Dr. John T. Sharp: After this organism became adapted to laboratory mediums it grew out as a typical alpha-hemolytic streptococcus. By the disk method tests showed that the sensitivity of this particular organism was fair to penicillin, poor to streptomycin and good to chloramphenicol. I think that this was the basis for the use of these particular drugs.

Dr. Chapman: May I ask if those sensitivity studies included polymyxin?

Dr. Sharp: This streptococcus was tested with polymyxin and demonstrated fair sensitivity. The *Ps. aeruginosa* isolated from the urine showed no sensitivity to the tetracyclines, poor sensitivity to chloramphenicol and fair sensitivity to polymyxin. The *Esch. coli* also isolated from the urine was not tested with polymyxin and showed no sensitivity to the tetracyclines, chloramphenicol or streptomycin.

Dr. Walter Bauer: A rubber-factory worker might be exposed to lead in the mixing room, where lead oxides are used.

Dr. Jacob Lerman: Such workers are more likely to be exposed to lead than to benzene.

Dr. Chapman: That is a good point; I did not know of the use of lead in this operation.

Dr. Edward F. Bland: I was not on the ward when this patient was in the hospital, but I recall giving quite a discussion at medical grand rounds about the importance of considering subacute bacterial endocarditis in any patient of this type who comes in with a murmur, anemia, a slight fever and this degree of renal impairment. We advised that streptomycin quickly be added to the armamentarium because by experience the enterococci are difficult to deal with under any circumstances. We thought this patient ought to be treated for subacute bacterial endocarditis as vigorously as seemed practicable. It is very comforting that Dr. Chapman and the others came to the same conclusion about the primary disease.

Dr. Lerman: I should like to ask Dr. Chapman if he considered that the patient had renal disease before this episode. The record states that six weeks before entry he had hypertension and uremia; that was about two weeks before the onset of the present illness.

Dr. Chapman: Perhaps I was misled by the opening remark that he was in good health until two months before admission. Farther along it was said that he had "no past history of rheumatic fever, chorea or growing pains"; nor had he ever had hematuria or any other symptoms referable to the genitourinary tract. I could do little more than accept this.

Clinical Diagnoses

Subacute bacterial endocarditis.
Embolic nephritis.
Uremia.

Dr. Earle M. Chapman's Diagnoses

Rheumatic heart disease, with aortic valvulitis and regurgitation.
Subacute bacterial endocarditis.
Embolic nephritis.
Uremic pericarditis.
Uremic colitis.

Anatomical Diagnoses

Acute and chronic pyelonephritis.
Glomerulitis, right kidney.
Hypoplasia, left kidney.
(Uremia) with uremic pericarditis.
Rheumatic heart disease, with aortic stenosis and regurgitation.
Acute endocarditis, aortic valve, terminal.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed that this man did have primary renal disease. The left kidney weighed only 10 gm., and the right 80 gm. (Fig. 1). I believe that probably the left was initially a hypoplastic kidney and the right normal. On section

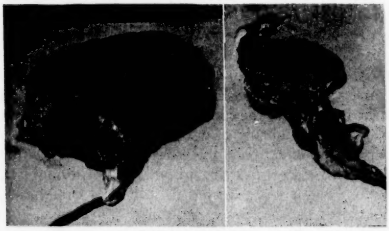

Figure 1.

there was no apparent renal tissue in the left kidney, which was tremendously hydronephrotic; the right was minimally hydronephrotic (Fig. 2). On microscopical examination the remnants of the left kidney showed a great deal of chronic inflammatory reaction and fragments of tubules, many of which were filled with colloid casts. Similar foci of colloid-filled tubules were present in the right kidney so that we have good evidence that there was pre-existing chronic pyelonephritis. There were no glomeruli in the left kidney, but in the right a fair number were present, many of which gave evidence of an acute glomerulitis with small areas of necrosis that were consistent with either an embolic type of nephritis or bacteremia.

The mitral valve was perfectly normal. There was marked interadherence between the cusps of the aortic valve at the commissures—a chronic, old process, producing aortic stenosis. The cusps were quite taut. There was no evidence of subacute bacterial endocarditis. We did find a tiny bit of adherent thrombus on one cusp that on microscopical examination was made up of fibrin and a few polymorphonuclear leukocytes and had an appearance that one frequently sees at autopsy when there has been sepsis — an acute terminal endocarditis. If this patient had had a subacute bacterial endocarditis that had been affected by

Figure 2.

the antibiotics, we would have been able to see a healing process in the valve with granulation tissue and organization. There was no evidence of that at all. Thus, although I think there was no subacute bacterial endocarditis, we have evidence of a bacteremia, which may well have come from the kidneys or from the severely diseased middle ears.

The lungs showed a severe pneumonitis, with hyalinization and fibrinoid changes in the alveolar walls such as we often see with uremia — some people like to call this uremic pneumonitis. There was pericarditis that was consistent with the uremia, and the small bowel showed much congestion and superficial erosion that might also be considered a uremic process.

Dr. Chapman: There was no evidence of myocardial infarction?

Dr. Castleman: No; there were some focal areas of old scarring, but no evidence of true myocardial infarction.

Dr. Allen G. Brailey: Obviously, this man had not been well up to two months before entry; perhaps a more carefully taken history might have yielded some evidence of renal disease earlier?

Dr. Yang Wang: For the sake of the record it should be added that by his own statement the patient was well until two months before admission, but he was a little bit cloudy. His wife stated that he had not been well for almost a year before admission. They both agreed, however, that he had never had any genitourinary symptoms.

Dr. Farahe Maloof: Was the spleen enlarged?

DR. CASTLEMAN: It weighed 150 gm. and could not have been felt.

DR. CHAPMAN: I think endocarditis with a normal-sized spleen has been described.

DR. MALOOF: How frequently do you see a large spleen with pyelonephritis?

DR. CASTLEMAN: Quite often. Some years ago Dr. Tracy B. Mallory looked up the cases with enlarged spleens and found that the largest spleens, except for the leukemias and the primary splenic diseases, were associated with chronic pyelonephritis; one weighed as much as 700 gm.

DR. DANIEL S. ELLIS: Is there anything in the laboratory data that would have helped to make the diagnosis of pyelonephritis, Dr. Bauer?

DR. BAUER: I do not know; I know so much about the case that any comment I could make would be influenced by that knowledge.

DR. CASTLEMAN: Is it not true, Dr. Bland, that most of the cases with renal disease associated with subacute bacterial endocarditis have a long course?

DR. BLAND: It is usually a long and often relatively quiet course in terms of fever. The striking feature is usually hematuria with increasing functional impairment, which dominates the renal picture. I think the course in this patient is a little clearer as we look back, but I still believe we more often miss subacute bacterial endocarditis in the older age group as the cause of anemia, renal involvement and ultimate uremia than the reverse.

CASE 40162

PRESENTATION OF CASE

First admission. A four-month-old female infant was brought to the Out Patient Department because of inability to move the legs normally.

The child was born at term by a normal delivery. The mother was well during pregnancy but had noted that fetal movements were less vigorous than those of her previous child, who was then a healthy girl of three years. The baby seemed normal and fed and swallowed well, but at the age of seven weeks the mother noted that the right leg was flexed at the hip and the child appeared unable to straighten it. She was taken to another hospital, where passive exercises seemed to bring about some improvement in the posture of the leg. Soon afterward, however, it was noted that the child moved very little; she could not lift her head or smile, the legs were almost immobile, and the arms appeared weak.

Physical examination showed a well nourished infant who lay almost motionless except for a few movements of the arms and facial muscles as she cried. There was no movement of the legs, and she could not hold up her head. The muscles were generally weak and flabby; passive hip movement was full, but there appeared to be slight restriction of knee flexion although extension was complete. The tendon reflexes were unobtainable. There was no withdrawal of the lower limbs on painful stimuli though the child responded by crying. The head was normal in size (50 cm. in circumference); the fontanelles, optic fundi and ears appeared normal, and there was no spinal deformity. The child was 67 cm. tall and weighed 6.0 kg.

Arrangements were made for her to be seen periodically in the clinic. A month later she was admitted to the hospital because of a "cold" that had begun two weeks previously. Soon afterward there were signs of difficulty in swallowing, and the breathing was affected because of pooling of secretions in the throat. The muscular condition was unchanged; she still did not move the legs and could not sit up or turn over, though she seemed to be making more grasping movements with the hands.

Physical examination revealed coryza, inflamed tonsils and infection of both tympanic membranes. The patient lay quietly, crying feebly. The legs did not move voluntarily; they were held abducted, flexed and externally rotated at the hips. The muscles were weak and flaccid, though there was a suggestion of more spontaneous arm movement than before; the muscular condition was much the same as that observed in the clinic.

The temperature was 99.6°F., the pulse 120, and the respirations 46. The blood pressure was 110 systolic, 60 diastolic.

The urine was normal except for a green reaction for sugar. The hemoglobin was 10.2 gm. per 100 cc., and the total white-cell count 18,400, with 28 per cent neutrophils, 15 per cent large lymphocytes, 50 per cent small lymphocytes and 7 per cent monocytes.

Lumbar puncture gave clear fluid containing a total protein of 36 mg. and a sugar of 88 mg. per 100 cc. and no cells. The pressure was not recorded. The fluid was sterile on culture.

Roentgenograms of the pelvis and both hips demonstrated soft-tissue changes (Fig. 1 and 2); a chest film disclosed no lung changes, and the heart was normal in size.

On the fourth hospital day the patient was given a subcutaneous injection of 0.125 mg. of prostigmine methyl sulfate, which was repeated forty-five minutes later, without significant effect. Treatment with penicillin and streptomycin was given, and the ear condition resolved. There was no change in the power of the extremities. She was discharged after thirteen days in the hospital.

Final admission (two months later). She was readmitted because of fever and cough. There had been no improvement in muscular power in the neck, trunk or limbs since the previous entry. A week before the second admission she began to have a mucous

discharge from the nose, followed by a weak cough and "gurgling in the chest." One day before admission she choked, turned blue and had a temperature of 102°F.

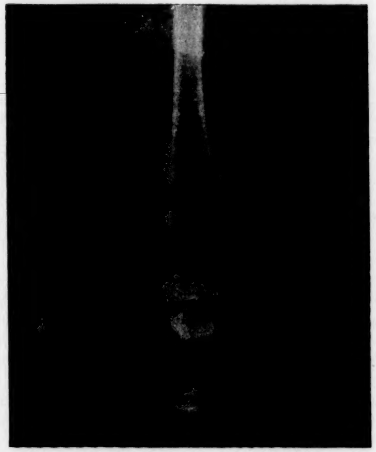

FIGURE 1. *Roentgenogram of the Upper Leg. The outline of the soft tissue of the thigh has been traced to show the wide band of fat, within which are thin, faintly discernible bands of muscle tissue.*

Physical examination revealed rapid, shallow and noisy respirations; breathing was largely diaphragmatic, and there was almost no intercostal movement. Auscultation of the chest showed multiple rhonchi. Both tympanic membranes were red and bulging. All four limbs were flaccid, and only occasional voluntary movements of the hands were observed; there was no movement of the upper limbs at the proximal joints or of the lower limbs, which were held flexed, abducted and externally rotated at the hip.

The temperature was 101.5°F., the pulse 120 and the respirations 26. The blood pressure was 100 systolic, 60 diastolic.

Urinalysis was not remarkable. A roentgenogram of the chest demonstrated no collapse or consolidation in either lung.

The patient was placed in an oxygen tent and was treated with systemic administration of penicillin; she showed some improvement, and on the fourth hospital day the left ear discharged serosanguineous fluid, which yielded abundant alpha-hemolytic streptococci on culture. Two days later myringotomy was performed on the right. By the twelfth hospital day both ears had stopped draining, and she seemed improved though there was still a remittent pyrexia. The next day the condition had deteriorated; both eardrums were red and bulging and bilateral myringotomy was performed, yielding mucopurulent fluid. On the fourteenth hospital day, while being fed, she suddenly

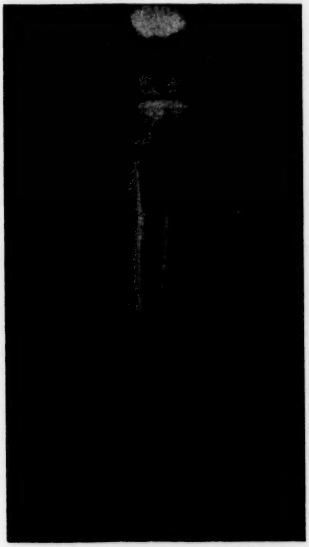

FIGURE 2. *Roentgenogram of the Lower Leg. The outline of the soft tissue has been traced.*

stopped breathing. There was no choking to suggest inhalation of milk. The pharynx was aspirated, and artificial respiration was given; despite these measures she died ten minutes later.

DIFFERENTIAL DIAGNOSIS

DR. BRONSON CROTHERS*: This is an utterly consistent history. The only thing that would make anyone pause is the fact that, for a short while, one leg was held in an odd position and was difficult to straighten out. Later, general weakness supervened. This patient demonstrated, as far as I can tell, all the changes of Werdnig–Hoffmann paralysis, which classically is a progressive disease in an infant who is weak from birth and finally deteriorates and dies. The alternatives that one always has to consider with a very weak baby are conditions such as arthrogryposis and mongolism, which are often spoken of as

*Senior consultant in neurology, Children's Medical Center.

"amyotonia" — and of course they are truly that — and the whole series of conditions such as Tay–Sachs disease, which is usually recognized as weakness in the early months. There was no sign of birth injury of the spinal cord, and the results of physical examination rule that out.

The extraordinary literature on Werdnig–Hoffmann paralysis, often called amyotonia congenita, has to be seen to be believed. Some physicians assert that the diagnosis of Werdnig–Hoffmann paralysis or progressive muscular atrophy of infancy ought to apply to almost all cases of weakness in children; others say that if one goes through the literature one can find a certain number of cases that present the general weakness and amyotonia described by Oppenheim[1] but that are not progressive and not familial. I think the bickering about whether amyotonia and Werdnig–Hoffmann paralysis are the same condition is generally regarded as pointless. I shall disregard this controversy and say that this infant had progressive muscular atrophy, with classic deterioration of the muscles and changes in the anterior-horn cells. I should be surprised, but not unduly so, if that was entirely wrong.

For me an important question that comes up in cases of this sort is whether any further investigation is either profitable or interesting. It is perfectly possible to do biopsies or to do electromyography. I think most of us who have done these have been disappointed in the results. The dilemma that we have often been placed in is to decide whether a baby of this sort has progressive muscular atrophy combined with spinal-cord damage or whether the child with progressive weakness who cannot stand or sit up has changes that are entirely muscular but no changes in the spinal cord. The latter cases fit no classification of dystrophy with which I am familiar; I am sure that they should not be included in this syndrome of Werdnig–Hoffmann paralysis. I am not alone in this because Brandt,[2] whose monograph on this and related conditions is probably the most extensive, has seen 2 patients like this in our clinic who clinically had this disease and yet whose spinal cords appeared to be perfectly normal so that he concluded that these were not cases of Werdnig–Hoffmann paralysis. The question whether the disease is entirely confined to muscle or whether it involves spinal cord is perhaps not entirely an academic one, but it is not important clinically or in relation to the advice one might give the family about further children.

The familial incidence of Werdnig–Hoffmann paralysis is well known. A number of children who have the disease may be born into a family, and every one of them will die at about the same early age. Another family may have a series of very weak children, fully as helpless as this, who survive perhaps six or seven years and then die. Once in a while there will be a variance between the length of time of survival of one child in a family as compared with another, but I have never seen one that lived ten years when one baby in the family died in the first year.

I should like to discuss another point, which is the advice to give parents who ask about birth control, since as I pointed out this disease may affect siblings within the same family. My opinion is that if a family is durable enough, intelligent enough and emotionally stable enough to want to take the chance of repeating this experience, I should approve; if the family is not willing to repeat the experience I should advise against further pregnancies. This child had the infantile form of this disease; as far as I know other children in the same family could be expected to have the same course. This family, if another affected child was born into it, would have an agonizing experience for a year or so. There is not much danger of releasing a damaging strain in the community because these children never propagate directly. There are reports in which other cases have occurred in other generations in the same family. I think I should give the same advice to parents whose child had Tay–Sachs disease.

DR. JOHN F. GIBBONS: I might show the films because there are definite findings that were not described when the films were originally interpreted. The left acetabulum is somewhat dysplastic, and I think there is a potential dislocation. The striking finding on these films is the fact that the soft tissues are definitely abnormal. There are huge amounts of subcutaneous fat in the legs and arms and thin muscle shadows, and even within the muscle shadows are scattered collections of fat. There is practically no muscle tissue in some areas (Fig. 1 and 2).

DR. RAYMOND D. ADAMS: I saw this child once in the Out Patient Department and once in the hospital. My impression was exactly like Dr. Crothers's — that this was an example of infantile muscular atrophy. It may be well to call attention to the fact that this as a general syndrome occurs not too infrequently in hospital practice. Clinically, the patient is fairly alert and the central nervous system seems to be developing all right, but he is extremely weak and moves the limbs very little. There is no impairment of visual or auditory function, and the child is normally receptive. Several different entities always have to be considered when this clinical syndrome presents itself. One, and the most serious, is the condition that has been discussed by Dr. Crothers. Another is infantile muscular dystrophy; families of them have been described. Then there are occasional children who appear to have a dystrophy but who later, to everyone's surprise, as they grow older improve and seem to recover. We do not know what disease all of them have, but by biopsy some have been shown to have a polymyositis. Probably, an occasional one has had an infantile poliomyelitis or polyneuritis. All these diseases cause weakness of the muscles and generally feeble movements. It is noteworthy that in in-

fantile muscular atrophy there is feebleness of movement and not paralysis. If the effect of gravity is removed, the patients can usually use most of the muscle groups.

Most of the confusion about these conditions probably arises from the fact that we have not been able to classify the cases that improve. They are the ones that raise the question about the amyotonia congenita of Oppenheim. I agree with Dr. Crothers that it is almost pointless to try to argue whether amyotonia congenita is the same as or different from infantile muscular atrophy. The first condition is so poorly described and so poorly documented that it hardly can be accepted as a clinical entity. Nearly all the cases that have been reported with pathological descriptions have been merely straightforward infantile muscular atrophy.

DR. BENJAMIN CASTLEMAN: Do the children with amyotonia congenita have spinal-cord disease?

DR. ADAMS: Usually, they do. In the cases that come to post-mortem examination there is some anterior-horn-cell loss as in infantile muscular atrophy. The changes in the nerves and muscles are typical of a denervation atrophy. The denervation atrophy occurs before muscles have fully developed so that there is a combination of fetal muscle with some fairly well developed units and some atrophied units.

CLINICAL DIAGNOSIS

Amyotonia congenita.

DR. BRONSON CROTHERS'S DIAGNOSIS

Werdnig–Hoffmann paralysis (infantile muscular atrophy).

ANATOMICAL DIAGNOSIS

Infantile muscular atrophy.

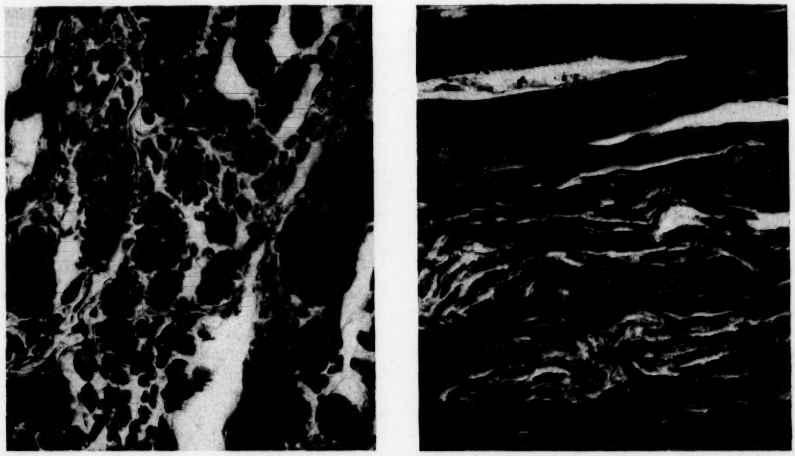

FIGURE 3. *Transverse* (A) *and Longitudinal* (B) *Sections of Muscle, Showing Clusters of Atrophied Fibers amid Fibers of Normal Size (PTAH Stain, High Power).*

PATHOLOGICAL DISCUSSION

DR. EDWARD P. RICHARDSON, JR.: Dr. Crothers was correct in the prediction that the findings would be typical of those described by Werdnig[3] and Hoffmann[4] in their articles on progressive muscular atrophy in childhood. There was extensive wasting of all the skeletal musculature, resulting from widespread degeneration of motor nerve cells in the spinal cord and brain stem, with the exception of the nuclei of the ocular muscles. The Betz cells of the motor cortex were far fewer in number than normally would be expected. Otherwise, there were no abnormalities in the brain.

The microscopical appearance of the muscle is typical of the condition. A cross-section view (Fig. 3A) shows the presence of groups of well developed fibers among severely atrophic fibers of small diameter. In a longitudinal section (Fig. 3B) these tiny fibers are seen to have a normal structural pattern of fibrils, with easily visible cross-striations. It is these fibers that have been described as "fetal"; they are best thought of as fibers that are atrophic because of lack

of motor innervation, secondary to the disease in the spinal cord.

A section of sacral cord stained for myelin sheaths showed degenerated anterior roots; numerous empty spaces in the anterior horns had been the site of motor neurons that had degenerated and disappeared. A high-power photomicrograph of a section stained for neurofibrils (Fig. 4) demonstrates the remains of a disintegrating anterior-horn cell with a normal neuron in the vicinity. Cells undergoing degeneration were rare in this case; for the most part, the motor neurons either were normal or had entirely disappeared.

DR. ALLAN M. BUTLER: Is there a difference in the creatinine excretion of such a child as this with muscular atrophy and a child with muscular dystrophy?

DR. ADAMS: The intolerance to ingested creatine and the low creatinine output are more pronounced in dystrophy than atrophy. I doubt, however, if these values would be normal in most cases of infantile muscular atrophy.

DR. BUTLER: Yes; a test dose of creatine gives a high creatine-creatinine ratio in dystrophy. But I am asking if the small muscle mass and lack of innervation of muscle in atrophy causes a diagnostically low twenty-four-hour urinary creatinine excretion.

DR. DAVID KAHN: Dr. Walton, can you answer that?

DR. JOHN WALTON: As Dr. Adams pointed out, most patients with the syndrome of amyotonia congenita have spinal muscular atrophy but undoubtedly a few are suffering from a benign congenital muscular dystrophy. The dystrophy cases of this type are very rare, and to my knowledge no chemical studies of this type have been done upon such infants. In general, however, the changes in creatine and creatinine are much more severe in myopathy, of whatever type, than they are in infantile muscular atrophy.

DR. KAHN: The other findings were a minimal interstitial pneumonitis and some evidence of terminal aspiration.

DR. ADAMS: These are the usual findings at autopsy.

FIGURE 4. *Anterior Horn of the Lumbosacral Cord (Cajal Stain for Axons and Neurofibrils, High Power). One degenerating and one normal motor neuron are clearly visible.*

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MEDICAL SERVICE STATIONS

DR. Robert Collier Page, who, as medical director of a large petroleum corporation, deals with medical-care problems in widely scattered parts of the world, has an excellent vantage point from which to view many aspects of the subject. In an address entitled "Expanding Horizons for Health Service," delivered at the annual meeting of the Massachusetts Hospital Association on January 26 in Boston to a group of hospital trustees and administrators, Dr. Page made a diagnosis, ventured a prognosis and prescribed treatment.

The diagnosis is familiar. Organized medicine and medical institutions are sick with complacency, inefficiency and apologetics. The prognosis is grave, with danger of loss of independence and of birthright. The physical environments in which diagnostic and curative medicine is largely practiced — namely, the hospitals — are "obsolete, costly and poorly managed." This opinion is advanced as both a symptom and a cause of present shortcomings and the prevailing overemphasis on curative medicine. The treatment advocated is the adoption of the concept of "constructive medicine," which means preventive, diagnostic, curative, rehabilitative and social medicine, integrated into a comprehensive, efficient health service. The concept of "constructive medicine" requires a specially created new physical environment: the medical service station. This facility has three contiguous sections: a large horizontal unit for ambulatory patients with emphasis on family practice, diagnostic, educational, health maintenance and home services; a small vertical unit for bed patients requiring definitive care of full-time specialists; and a moderate-sized convalescent unit emphasizing rehabilitation and maximum self-help.

Dr. Page extrapolates the curve of advancing functional specialization in medicine and the paramedical professions, and has suggested the design of the environment in which this functional specialization can fulfill its destiny and deal effectively with comprehensive promotion of health rather than the episodic treatment of illness.

The proposed economics of the medical service station are those of private industrial enterprise. Although it is fully recognized that the Government now plays a large part in health and medical care the concept of constructive medicine efficiently organized in a purposefully designed physical plant is advanced by Dr. Page as the necessary way to avoid complete transfer of health and medical care to a governmental bureaucracy by a justifiably impatient public.

The opinions of Dr. Page are stimulating, provocative and worthy of attention. More important, however, is this additional evidence of the willingness of hospitals and doctors to undergo a searching self-examination and evaluation.

NEW VIRAL AGENT FROM ACUTE RESPIRATORY DISEASES

THE development of suitable technics for the study of the common cold and other simple acute respiratory infections has been notoriously unsuccessful, in spite of the extensive and costly efforts of several groups of outstanding investigators in this country and in England in the last several years. All the different technics that proved useful with other viruses have failed to achieve unequivocal success when applied to the common cold. To be sure, some colds have been produced with cultures of the "cold virus" in fertile hens' eggs, but, unfortunately, materials from uninoculated eggs have not given such uniformly negative results as other control materials and the proportion of positive results has not been uniformly high, making the data hard to interpret.

A degree of success seems now to have been achieved in some of the latest attempts to use tissue-culture methods based largely on technics developed for other viruses by Enders and his co-workers at the Children's Medical Center in Boston. Workers in the Common Cold Unit at the Harvard Hospital in Salisbury, England, propagated a common-cold virus through 10 serial cultures of embryonic human lung. However, the colds were induced with these cultures in only 10 per cent of the volunteers with material from the fourth to the tenth passages, and none were induced by materials from subsequent passages.[1] The major difficulty, as in some of the earlier experiments using chick embryos, was in maintaining the virus through continuous passages in the cultures. This may now have been achieved in two separate laboratories in the United States.[2,3]

Two independent groups of workers recently reported the cultivation of apparently new viral agents from the human respiratory tract that they were able to transmit serially in tissue cultures. Rowe and his collaborators,[2] working at the National Microbiological Institute and at Johns Hopkins University School of Hygiene and Public Health, found a cytopathogenic agent in roller-tube cultures of human adenoid tissue that they transmitted serially through other tissue cultures. They used cultures of three types of tissue: adenoid and embryonic tissue and HeLa cells. The last, consisting of cells of human epidermoid cancer cultivated en masse and maintained in vitro since their derivation in February, 1951, were recently shown to support the multiplication of all three types of poliomyelitis virus.[4]

Culture fluids of 14 adenoids demonstrating this degeneration were transferred by these workers to fresh cultures of adenoids, human embryonic tissue or HeLa cells. In 13 cases characteristic changes were produced in the recipient cultures. One of the isolations of this agent was obtained from an adenoid that degenerated on the eighth day of culture; this strain has now been carried through a total of 17 passages: the first in adenoid, 1 in the trachea of the human embryo, and the last 15 in HeLa cells, with production of typical changes in every passage. Degeneration of the seventeenth passage tissue occurred a day after infection with fluid, representing a theoretical dilution of the original adenoid fluid of 10^{-32}. Fluid of the eleventh passage when passed to cultures of human fetal trachea reproduced a typical cellular degeneration after three days. Similarly, other strains of the agent have been carried without difficulty through serial passages and have consistently reproduced the degeneration. In both human embryonic skin and HeLa-cell cultures the agent has been found to reach a titer in the supernatant fluid of more than 10^5 infectious units per cubic centimeter when titrated in HeLa cells.

From this evidence it appears that an unidentified and possibly new tissue-culture cytopathogenic agent has been repeatedly isolated from human adenoids undergoing spontaneous degeneration in tissue culture. The filterability and the inability to cultivate the agent on bacteriologic mediums, as well as to demonstrate organisms in stained tissue-culture preparations, indicate that the agent is a virus or rickettsia. These workers have tentatively designated the agent as the "adenoid degeneration agent," abbreviated as "AD agent." That this agent is derived from the adenoid tissue rather than the nutrient medium was indicated by the fact that some adenoids and all human embryonic tissues cultivated in identical mediums and at the same time have not undergone degeneration although they are susceptible to infection with the agent. Also, repeated attempts to isolate the agent from adenoid cultures not demonstrating degeneration have been uniformly unsuccessful. These studies are continuing, and attempts are being made to determine the relation of the agent to the adenoids and its possible role in human disease, particularly upper respiratory infections.

Another report dealing with a similar, or possibly the same, agent comes from the Army Medical Service Graduate School, where Hilleman and Werner[5] isolated the agent in the course of studies on the etiology of some noninfluenzal infections occurring during an epidemic of acute respiratory illnesses at Fort Leonard Wood, Missouri, during the winter of 1952-53. These workers also utilized cultures of the HeLa cells, from which they recovered a microbial agent from throat washings in a patient with a respiratory infection that they called "primary atypical pneumonia." Their agent also multiplied in these cell cultures, producing obvious cytopathogenic changes, but it did not cause any changes in common laboratory hosts. The patient whose throat washings yielded the virus demonstrated only specific neutralizing antibodies for this agent, but others yielding positive results manifested complement-fixing antibodies for this virus as well. Antibodies for the new agent developed in the patients in the epidemic who had "primary atypical pneumonia" or undifferentiated acute respiratory disease, but not in those with proved infection with influenza A′. However, serums from all the patients with positive serologic findings with the new virus gave negative findings when tested for infection with influenza A, B and C, for cold isohemagglutinins and for *Streptococcus MG* agglutinins. Antibodies against the new agent were also found in a significant portion of the general population, suggesting general exposure to it.

Dr. Hilleman repeated the basic observations in Dr. Dingle's laboratory at Western Reserve University, where he again showed the cytopathogenic effect for HeLa cells in cultures prepared there, as well as in his own laboratory. Neutralization tests with known positive and negative paired serums were also carried out with the cultures and the reagents of the two sources, and identical results were obtained. When

Hilleman and Werner[3] became aware of the report of Rowe and his co-workers[2] they performed tests in both laboratories that gave presumptive evidence of an immunologic relation between the agents isolated.

It therefore seems possible that at last a viral agent has been isolated that may be etiologically related to cases of simple acute respiratory infections and that can easily be maintained in tissue cultures. The way now seems open for a vast expansion of studies on the common cold and related infections.

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THE SHOUTING AND THE TUMULT

A WEEK or two after the hubbub over the unsatisfactory response by physicians to emergency calls had partially subsided, an irate patient in Dorchester telephoned the operator that if a doctor was not at his bedside within fifteen minutes he intended to call the newspapers. The public has also shown interest and concern in what the Massachusetts Medical Society is going to do about the allegation of misconduct on the part of certain registered practitioners in connection with insurance claims.

The average physician who is not derelict in either his ethical or his professional responsibilities may be inclined to react to an inflamed public interest in his conduct with the conviction that the newspapers and the Society would both be better occupied if the former confined themselves to printing news instead of scandal and the latter retired to its old obscurity in a corner of the Medical Library where the fellows might listen to the report of the Committee on Arrangements and select the Shattuck lecturer in peace.

Unfortunately, perhaps, one is not living in the medical world that existed at the turn of the century. The Massachusetts Medical Society is not a detached professional group like the Association of American Physicians; it has become a public-service organization, and if in the public mind it is responsible for the activities of its members in general, it has no course but to accept the responsibility actively. However, it is desirable that newspapers in their turn should feel obligated to investigate before broadcasting charges that physicians have been neglectful of their duty.

The Society will without doubt continue to screen all applicants for fellowship with great care, and to punish or expel any proved miscreants. Fortunately, it is still headline news when a doctor is merely suspected of being unfaithful to professional standards that people have learned to respect and take for granted.

HEARTS AND FLOWERS

NOT until the issue of April 8 did the circulation department of the *Journal* this year perform the sad rite of dropping from the lists those 698 fellows of the Massachusetts Medical Society who, up to that time, had failed to pay their annual assessment. The fact that the bill was sent by the Treasurer early in January is considered by some to have constituted ample notice of the indebtedness; in addition, this delayed action gave the absent-minded colleagues an extra period of grace, since the annual housecleaning takes place usually in March.

Unfortunately or otherwise, the *Journal* has never found itself in the position of being able to go on printing the accustomed number of copies after this fateful step has been taken, so what is lost is lost forever. Perhaps it is a cheering factor that the forgetful fellows will be spared the anguish of reading this announcement; unless they frequent some library they will never know that they are missing, in this very issue, a special article on "The Impact of Disease on American History" and the beginning of a progress report on "The Common Cold." They will not realize that on May 6 the regular weekly brain washing will be augmented by the first instalment of a tripartite paper on "Digitalis Therapy," and a "Doctor Afield" dealing with the great Maimonides, and so forth, ad infinitum.

It is small comfort for the editors of the *Journal* to ruminate on the saving effected by each $5.00 Society subscription that does not have to be fulfilled. This apparent fiscal indifference is born of the fact that, although the actual annual cost of fulfilling each subscription amounted last year to $7.78, the difference was borne with fortitude bordering on cheerfulness by the *Journal's* loyal advertisers. As a result the *Journal's* brand-new motto is *Non conservare sed servare.*

It is earnestly hoped that those who read this exhortation will remind those who have deprived themselves of reading it (if they can be recognized) that neither the treasurer of the Society nor the editors will be able to say "Mission accomplished" until all are back in the fold.

A man by the name of Brown recently died in convulsions, and subsequent post-mortem examination showed that his death was caused by eating cloves, which he had been habitually using for a long time instead of tobacco.

BOSTON M. & S. J., *April 26, 1854*

MASSACHUSETTS MEDICAL SOCIETY

COOK — Philip H. Cook, M.D., of Worcester, died on March 25. He was in his seventy-seventh year.

Dr. Cook received his degree from Harvard Medical School in 1903. He was librarian, Worcester Medical Library, and formerly president of the Worcester District Medical Society and the New England Roentgen Ray Society. He was a member of the staffs of the Worcester City, Memorial and Hahnemann hospitals, an associate fellow of the American Medical Association, a fellow of the American College of Radiologists and a member of the American Roentgen Ray Society.

He is survived by five cousins.

KLEIN — Armin Klein, M. D., of Newton, died on April 3. He was in his sixty-second year.

Dr. Klein received his degree from Harvard Medical School in 1917. He was acting chief of orthopedic surgery, Beth Israel Hospital, professor of clinical orthopedic surgery, Tufts College Medical School and formerly chief of orthopedic surgery, Massachusetts General Hospital. He was a fellow of the American Medical Association and the American Academy of Orthopaedic Surgeons and a member of the American Orthopaedic Association.

He is survived by a daughter, two sons, a brother and five grandchildren.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

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ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Salem	May 3	Paul W. Hugenberger, M.D.
Gardner	May 4	Carter R. Rowe, M.D.
Haverhill	May 5	William T. Green, M.D.
Greenfield	May 6	Charles L. Sturdevant, M.D.
Lynn*	May 10	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	May 13	George W. Van Gorder, M.D.
Lowell	May 14	Albert H. Brewster, M.D.
Springfield	May 18	James D. Fisher, M.D.
Pittsfield	May 19	Edward J. Coughlin, Jr., M.D.
Worcester	May 21	John W. O'Meara, M.D.
Fall River	May 24	David S. Grice, M.D.
Hyannis	May 27	Paul L. Norton, M.D.

RHEUMATIC-FEVER CLINIC	DATES
North Reading	May 4, 11, 18, 25
Fitchburg	May 5, 12, 19, 26

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

REGARDING THE FRAGILE MALE

To the Editor: My attention has been called to the editorial in the December 31 issue of the *Journal* entitled "The Fragile Male." I appreciate very much the reference to my article on this subject in the *Journal of the Florida Medical Association* (38:553, 1952).

I feel very strongly that this matter should be of concern to the medical profession throughout the country. The editorial mentioned the possibility of different conditions in Florida and in the rest of the country that may have a bearing on this subject. Actually, there does seem to be some such difference, as indicated in Table 1.

TABLE 1. *Age-Adjusted Death Rates by Race and Sex and Ratio of Male to Female Death Rates, United States and Florida (1920, 1930, 1940 and 1950).*

YEAR	RATE* WHITE MALES	WHITE FEMALES	NONWHITE MALES	NONWHITE FEMALES
United States:				
1920	14.2	13.1	20.4	21.0
1930	12.8	10.6	21.0	19.2
1940	11.6	8.8	17.5	14.9
1950	9.7	6.5	13.5	10.9
Florida:				
1920	13.8	12.1	19.5	18.8
1930	13.1	9.8	23.3	19.5
1940	11.5	7.5	20.1	15.8
1950	9.1	5.6	14.7	11.0

	DIFFERENCE BETWEEN MALE AND FEMALE RATES WHITE %	NONWHITE %
United States:		
1920	+8	−3
1930	+21	+9
1940	+32	+17
1950	+49	+24
Florida:		
1920	+14	+4
1930	+34	+19
1940	+53	+27
1950	+62	+34

*Total United States population of 1940 used as standard.

I have no idea why there should be a greater difference in the mortality of males and females in Florida and elsewhere. However, in Florida's defense it will be noted that, at least among whites, the age-adjusted death rates are lower for both sexes. To me the most interesting and alarming fact is the steadily widening differences in mortality between the two sexes throughout the country.

WILSON T. SOWDER, M.D.

Jacksonville, Florida

REGARDING PERCUSSION OF THE SPLEEN

To the Editor: I was happy to see percussion of the spleen re-emphasized by Dr. Robert K. Nixon, Jr., in the January 28 issue of the *Journal*. The method has never been abandoned in the Latin countries, and we teach it routinely as a valuable way of examining an organ that, hidden away in its costal recess, still escapes nonclinical means of exploration.

It is regrettable, however, that Dr. Nixon should cite only American textbooks as a basis for the statements that percussion of the spleen "is mentioned only in passing in all modern standard works on physical diagnosis" and that "the consensus has been that the method is of little value." In the following three *modern* non-American textbooks in my library (French, Spanish and Argentine, respectively) the procedure is clearly and extensively described, and the right recumbent position is recommended, particularly by Surós

and by Padilla: Sergent, E. *Traité élementaire d'exploration clinique médicale* (Paris: Masson et cie, 1950); Surós, J. *Semiología médica y técnica exploratoria* (Madrid: Salvat, 1953); and Padilla, T. *Semiología del riñón, del bazo y de la sangre* (Buenos Aires: El Ateneo, 1948).

MARCEL ROCHE, M.D.
Profesor Agregado Cátedra de Clínica Semiológica
Universidad Central
Caracas, Venezuela

PHYSICIANS AND POLITICIANS

To the Editor: The editorial in the February 18 issue of the *Journal* entitled "Physicians or Politicians?" was either thoughtlessly written or inserted to make the fellows think as well as pray.

Although parenthetically stating that the majority of the councilors had approved the legislation it implied that there was doubt whether as physicians we should concern ourselves with the Bricker amendment since there was only a potential and indirect effect on the practice of medicine. The question in the title must be answered by the statement that, being physicians, we are not relieved of being politicians as are all citizens and as were the five doctors who signed the Declaration of Independence.

It is suggested that the writer of the editorial consult Webster regarding the definition of a politician and consider if he was prudent, sage and wise to use the columns of the official organ of the Massachusetts Medical Society to express his opinion, when the members of the Council had expressed theirs.

ROBERT M. HOLLAND, M.D.
West Roxbury, Massachusetts

Note: The exercise of that freedom of the press with which democracy in this country is so closely identified should be guided by good taste, mature judgment and mutual respect between the proprietors and editors of a publication. It has long been the belief of the editors of the *New England Journal of Medicine* that the fellows of the Massachusetts Medical Society do not wish other than to maintain for their own press, within these reasonable limits, that freedom that they surely regard so highly as the prerogative of other publications. — ED.

BOOK REVIEW

A History of Psychoanalysis in America. By C. P. Oberndorf, M.D. 8°, cloth, 280 pp. New York: Grune and Stratton, 1953. $5.00.

In defining the term "psychoanalysis," Dr. Oberndorf uses the definition to which he states he personally is content to subscribe. It is Freud's own, as quoted by Ernest Jones: "Psychoanalysis is simply the study of processes of which we are unaware, of what, for the sake of brevity, we call the 'unconscious', by the free association technique of analyzing observable phenomena of transference and resistance."

From the pinnacle of his seventy years, Dr. Oberndorf has viewed the development of psychoanalysis in the United States from its inception to the present day. He is rich enough in years and sound enough in memory to give a personal account of psychiatry and its relation to medicine at the turn of the century. He traces the beginnings of Freudian psychoanalysis so delicately that one cannot doubt that he is equally fair in recognizing other philosophic schools, such as that of Edward Hartmann, who wrote a book entitled "Philosophy of the Unconscious" in Berlin in 1867. One need not fear that Dr. Oberndorf will place Freud in the falsely messianic position into which many have thrust him. With remarkable precision he shows how psychoanalytic theory became crystallized and reached America.

The division of this book into the chapters Dr. Oberndorf has chosen gives a splendid guide to an organization of his subject. In the first place he discusses several novelists, particularly Hawthorne and Holmes, in relation to advanced awareness of what later became Freudian theory. In the course of this discussion, he builds a solid concept of the growth of psychologic understanding among the reading public in the United States.

Dr. Oberndorf naturally emphasizes the growth of psychoanalysis in New York City, beginning with its origin at Manhattan State Hospital, where he himself worked. He describes clinical practice and the informal organization of psychoanalysis from 1910 to 1920. He outlines its expansion in a fascinating manner, perhaps with too much modesty. It was between the years 1910 and 1920 that psychoanalysis created a definite impact on education and on the public. Dr. Oberndorf separates the wheat from the chaff in this period with an experienced hand.

He returned to Vienna for further psychoanalytic training in 1921-22. In this part of the book he gives the reader stimulating glimpses of the currents and cross-currents then flowing in that turbulent stream. Here, too, is another fragmentary portrait of Freud himself.

He treats the "terrible thirties" in a separate division, showing how the disengagement of psychoanalysis from its parent stem gradually began and was furthered in this country as Western Europe staggered blindly toward total war.

The description of the stormy years in psychoanalysis under New York leadership in the period 1920 to 1930 displays remarkable objectivity and gives credit where credit is due. Dr. Oberndorf shows an extraordinary (almost photographic) memory for names, dates and places and the events that transpired. As a study in the growth of a new thought movement and an abstract of medical politics, his book is extraordinary in itself.

The development of formal instruction in psychoanalysis is treated with utmost impartiality. The author shows the pressures on the subject from different areas, treating all with an Olympian objectivity.

He is more than careful in his observation of the changes that have taken place in the development of psychoanalysis from the early, classic psychoanalysis as advocated by Freud, including Freud's strong advocacy of lay analysis, through the present changes and modifications that took place in the period 1930-1940, manifested especially in the formal instruction in that subject and the increasing development of institutes in American cities now numbering about fifteen.

Perhaps the most interesting chapter in the book is the last, which considers the changes in psychoanalytic conceptions developing in the United States after World War II. The author's comments on current tendencies are liberal, almost to the extreme, but possibly they are also prophetic. Perhaps when he begins to consider future steps toward mental health, he tends to over-rate the intellectual level of the electorate. His capacity to give and withhold credit without malice is exceptional. He is able to view even himself without a halo. One sees in his discussion of the uses and abuses of psychoanalysis, and of its trends, an inquisitive, independent mind. He seems to share the pragmatism that he regards as one of the bases for the acceptance of psychoanalysis in America. He is noncaustic, but never mushy.

Very few writers have documented their lifework so carefully and so creditably as Dr. Oberndorf. This book is far more than a careful, external survey of the field of psychoanalysis in America. It not only follows the facts, as the author sees them, and the broad trends but also expresses his personal views. There will undoubtedly be many who disagree with his opinions, for, as he says himself, there are as many attitudes toward psychoanalysis as there are psychoanalysts. Covering, as it does, fifty years of growth, his book has documentary as well as reportorial value.

This is a book that every physician will want to own and read carefully when he considers the relation of his own specialty to the all-embracing field of psychoanalysis that now stands pre-eminent in its survey of problems of the mind and body.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Resuscitation of the Newborn. By Joseph D. Russ, M.D., assistant professor of pediatrics, Tulane University of Louisiana School of Medicine, and senior pediatrician, Touro Infirmary, New Orleans. 8°, cloth, 55 pp., with 7 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $2.50. (Publication No. 193, *American Lecture Series.)*

This small monograph considers the various aspects of neonatal asphyxia on the basis of the author's personal experience with 2000 resuscitations, performed since 1938. The pertinent literature is reviewed, and a bibliography of 139 references is appended to the text.

Diseases of Women. By ten teachers. Under the direction of Frederick W. Roques, M.D., M.Chir., F.R.C.S., F.R.C.O.G. Edited by Frederick W. Roques, John Beattie and Joseph Wrigley. Ninth edition. 8°, cloth, 480 pp., with 177 illustrations. London: Edward Arnold and Company, 1953. $6.50. (Distributed by Williams and Wilkins, Baltimore.)

The first edition of this standard English book was published in 1919, and 16 printings of 9 editions have been made to date. Naturally, the contributors have changed, but the number of 10 authorities has been maintained. The chapters on the endocrine glands, the hormones and the physiology of the menstrual function have been completely, and those on the infections and venereal diseases largely rewritten. It is a practical book without reference to the literature. There is a good index. The printing was done in Great Britain, and the publishing is excellent.

Modern Clinical Psychiatry. By Arthur P. Noyes, M.D., superintendent, Norristown State Hospital, Norristown, Pennsylvania, and associate professor of psychiatry, Graduate School of Medicine, University of Pennsylvania. Fourth edition. 8°, cloth, 609 pp. Philadelphia: W. B. Saunders Company, 1953. $7.00.

This standard book on psychiatry was last published in 1948. In this new edition descriptive psychiatry has not been altered to any extent, but the author has concentrated on the principles of basic psychiatry and the application of genetic and dynamic factors to clinical psychiatry. The classification of mental disorders is different from those used in previous editions. This edition uses the standard nomenclature officially adopted by the American Psychiatric Association. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

The Physics of Radiation Therapy. By Harold E. Johns, M.A., Ph.D., F.R.S.C., professor of physics, University of Saskatchewan, and physicist, Saskatchewan Cancer Commission, Saskatoon, Saskatchewan, Canada. 4°, cloth, 286 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1953. $8.50. (Publication No. 116, *American Lecture Series.*)

This new and up-to-date monograph is intended for daily use in radiation therapy. There is a comprehensive discussion of the x-rays and their physics, and chapters on radium, high-energy devices and artificial radioactivity. The appendixes present tables of depth dose and isodose and spectral distributions. Lists of references are appended to the chapters, and there are author and subject indexes. The book is recommended for all medical libraries and to all interested persons.

NONCLINICAL NOTES

HEART OF GOLD

Dr. Howard B. Sprague, of Boston, clinical associate in medicine at the Harvard Medical School and past president of the American and Massachusetts Heart associations, has been presented with the Gold Heart Award of the American Heart Association.

DR. SIDNEY FARBER

Dr. Sidney Farber, professor of pathology of Harvard Medical School at the Boston Children's Hospital, and scientific director of the Children's Cancer Research Foundation, has received a Katharine Berkan Judd award of the Memorial Center and the Sloan-Kettering Institute for Cancer Research in New York.

The award was made for his "epoch-making studies in the use of chemotherapy for the treatment of cancer, particularly acute leukemia in children."

NOTICES

BIBLIOGRAPHIC REFERENCES ON MELANOGENESIS

A number of requests have been received for references pertaining to the editorial "Melanin," published in the November 26, 1953, issue of the *Journal.*

The editorial was based largely on experimental material set forth in the following papers:

Lerner, Aaron Bunsen, and Fitzpatrick, Thomas B. Biochemistry of melanin formation. *Physiol. Rev.* **30**:91-126, 1950.

Lerner, Aaron Bunsen, and Fitzpatrick, Thomas B. Control of melanogenesis in human pigment cells. In *Pigment Cell Growth.* New York: Academic Press, 1953. Pp. 319-333.

Fitzpatrick, Thomas B., and Lerner, Aaron Bunsen. Biochemical basis of human melanin pigmentation. *Arch. Dermat. & Syph.* **69**:133-149, 1954.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the auditorium, Jimmy Fund Building, May 11 at 7:30 p.m. The program, to be presented by the Undergraduate Assembly, Harvard Medical School, is as follows:

The Effect of Pituitary Growth Hormone on Tumor Growth and Metastasis. Douglas Holyoke and Sumner Wood, Jr. (fourth year).

Effects of Pinealectomy on Ovary Weights in Immature Rats. Julian I. Kitay (fourth year).

Metabolism of C^{14}-Labeled Glycerol and Pyruvate by Liver in Vitro. Bernard Landau (fourth year).

Observations on the Nature of Muscle Cramps. Forbes H. Norris (third year).

The Shift of the Acid-Base Titration Curve of Rhodopsin after Light Bleaching. Charles H. Radding (third year).

Some Studies on the Effect of Parathyroidectomy and Dietary Calcium Restriction on the Calcium Metabolism of Lactation in the Rat. Svein U. Toverud (fourth year).

Histochemical and Pharmacological Studies on Myasthenia Gravis. Sumner I. Zacks (third year).

After this program the Soma Weiss Award will be presented by the faculty committee.

NEW ENGLAND CARDIOVASCULAR SOCIETY HENRY JACKSON LECTURE

The Henry Jackson Lecture, sponsored by the New England Cardiovascular Society, will be delivered by Dr. Albert Szent-Györgyi, director, Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts, in Morse Auditorium, Museum of Science, Boston, on Monday, May 10 at 8 p.m. The topic will be "Problems of Muscle Contraction." Physicians and students are invited.

CUTTER LECTURE

Dr. Thomas Parran, dean of the Graduate School of Public Health, University of Pittsburgh, will deliver the Cutter Lecture on Preventive Medicine of the Harvard School of Public Health in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, on Thursday, May 6. His subject will be "Contributions of Public Health to the Control of Chronic Disease."

MASSACHUSETTS TRUDEAU SOCIETY AND MASSACHUSETTS TUBERCULOSIS AND HEALTH LEAGUE

The annual meeting of the Massachusetts Trudeau Society will be held in conjunction with the Massachusetts Tuberculosis and Health League at the Sheraton Plaza Hotel, Boston, April 30 at 2 p.m. The following program will be presented: "Etiologic Factors in Carcinoma of the Lung," Dr. Ernest L. Wynder; "The Treatment of Miliary and Meningeal Tuberculosis," Dr. Louis Weinstein; "The Role of Pulmonary Insufficiency in Mortality and Incapacity Following Surgery for Pulmonary Tuberculosis," Dr. Edward A. Gaensler. Interested physicians are invited.

ARGENTINE CONGRESS OF THORACIC SURGERY

The second Argentine Congress of Thoracic Surgery and the seventh Argentine Meeting of Thoracic Surgery will be convened by the Argentine Society of Thoracic Surgery (sponsored by the Chair of Thoracic Surgery, Faculty of Medical Sciences, University of Buenos Aires) in Buenos Aires from August 17 through 20. Further information may be obtained from the Secretaría del Congreso, Caseros 2153, Buenos Aires, Argentina.

SOCIETY MEETINGS AND CONFERENCES

April 23–28. Consultation Clinics for Crippled Children. Page 490, issue of March 18.
April 23–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.
April 24. Boston City Hospital Alumni Association. Page 491, issue of March 18.
April 24. Massachusetts Association of Medical Technologists. Page 540, issue of March 25.
April 26. Massachusetts Heart Association. Kidney Section. Page 585, issue of April 1.
April 26–May 2. International College of Surgeons. Page 492, issue of March 18.
April 27. Hampden District Medical Society. Page 620, issue of April 8.
April 28. New England Medical Center House Officers' Association. Page 664, issue of April 15.
April 28. Massachusetts Society of Examining Physicians. Page 585, issue of April 1.
April 28. Middlesex South District Medical Society. Page 585, issue of April 1.
April 29 and 30. New York Academy of Medicine. Eastern States Health-Education Conference. Page 491, issue of March 18.
April 29, 30 and May 1. American Goiter Association. Hotel Somerset, Boston.
April 29, 30 and May 3–7. Yale University Silliman Lectures. Page 585, issue of April 1.
April 30. Massachusetts Trudeau Society and Massachusetts Tuberculosis and Health League. Notice above.
May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.
May 3. Civil Defense Exercise. Page 664, issue of April 15.
May 3–26. Consultation Clinics for Crippled Children. Page 705.
May 6. Cutter Lecture. Notice above.
May 10. New England Cardiovascular Society. Henry Jackson Lecture. Notice above.
May 10–12. Institute of Industrial Health. Page 491, issue of March 18.
May 11. Harvard Medical Society. Page 707.
May 12. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)
May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.
May 12. New England Obstetrical and Gynecological Society, Spring Meeting. Longmeadow Country Club, Springfield
May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.
May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.
May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.
May 17–23. National Tuberculosis Association. Page 663, issue of April 15.
May 18–20. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
May 27 and 28. New York Surgical Division of International College of Surgeons. Page 585, issue of April 1.
May 27–29. American College of Cardiology. Page 585, issue of April 1.
May 31–June 3. American Urological Association. Page xvii, issue of July 23.
June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.
June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.
June 14–16. American Neurological Association. Page 540, issue of March 25.
June 15–18. Medical Library Association. Page 491, issue of March 18.
June 17–19. American Geriatrics Society. Page 266, issue of February 11.
June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.
June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.
June 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.
July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.
July 23–29. International Cancer Congress. Page 914, issue of November 26.
July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.
August 17–20. Argentine Congress of Thoracic Surgery. Notice above.
September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.
September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.
September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.
September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.
October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 29

THURSDAY, APRIL 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
9:00 a.m. American Goiter Association. Hotel Somerset, Boston.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
11:00 a.m. Thoracic Conference. Medical and Surgical Aspects of Mitral Insufficiency. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Treatment of Peripheral Arterial Occlusion. Dr. Stanford Wessler. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, APRIL 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
9:00 a.m. American Goiter Association. Hotel Somerset, Boston.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

(Notices concluded on page xxiii)